ON THE PATHOGENESIS OF CANCER *

D. W. SMITHERS
M.D. Cantab., F.R.C.P., F.F.R.
DIRECTOR OF THE RADIOTHERAPY DEPARTMENT,
THE ROYAL MARSDEN HOSPITAL AND INSTITUTE OF CANCER RESEARCH:
ROYAL CANCER HOSPITAL, LONDON, S.W.3

AN International Cancer Conference was convened by the British Empire Cancer Campaign in London in 1928. Later, the present series of congresses under the International Union Against Cancer was started, the seventh of which was held last July—30 years after the previous London meeting. I have chosen as the title of this lecture that taken by Dr. Archibald Leitch when he addressed the 1928 conference, On the Pathogenesis of Cancer. Leitch was a graduate of Glasgow University and gave the first Weild lecture to the Royal Faculty of Physicians and Surgeons in 1926; he was also the director of the research institute which was then part of the Cancer Hospital in London where I have been working for the past 23 years. Since his lecture was given there have been considerable changes in outlook on the origins and development of these growth disorders, and in saying something about those changes I shall suggest that it is time we accepted their implications.

A Specific Irreversible Change in Individual Cells?

In 1928 emphasis in cancer research lay on the search for a specific growth substance which would prove to be the direct cause of cancer. It was thought that the isolation of this chemical agent might lead to understanding and prevention, if not to cure.

Theory had not been well supported by experiment, and it was no doubt this consideration which led Leitch to select the experimental induction of cancer in rats and the demonstration of the presence of a transmissible filterable tumour agent in fowls as the two outstanding contributions to cancer research in the previous twenty years. Through all the long years of endeavour to extract a growth substance from malignant cells, the filterable agent had been the only success to encourage those stubborn adherents to simple theories of cancer and its causation who persisted in believing that they were dealing with a specific disease rather than a generic appellation. Leitch himself, who had a broad outlook on the problem, favoured the view that tumour formation was the result of an overaction of a normal cell stimulant rather than of some entirely new provocation which attacked from without. The search for a special stimulant to growth was, however, much in his mind. He wrote of growth as though to him it was naturally controlled and unnaturally excited. The cause of cancer was expected to be revealed as a specific chemical substance. He concluded his address to the cancer conference by saying that his work in experimental carcinogenesis suggested that

> the "growth substance" for which we have looked so long in malignant growths may be within the range of experimental investigation.

Altered Behaviour Patterns in Different Tissues?

Thirty years have passed. Interest in the first experimental rat tumour induction by a parasite, which had seemed so important to Leitch, has declined as the ease with which animal tumours may be induced by a great variety of means has grown. Not a single human invasive tumour has ever been shown to be due to a virus. The carcinogenic hydrocarbons have been discovered and isolated in Leitch's own laboratory by his successors under Kennaway. The two-stage mechanism of tissue response to carcinogenic substances has been demonstrated, and the list of carcinogens has grown to such formidable proportions that graver difficulties than ever obstruct the view of cancer as a disease caused by a specific extraneous growth substance. Chemicals which can lead to tissue overgrowth abound; many regularly produce tumours experimentally in animals. A few of the most active which were found to be responsible for certain human tumours have been reduced in our environment, so that some progress in tumour prevention resulted from this work—but others have come to take their place and affect a much larger section of the population. The hoped for new understanding did not follow these chemical advances; the single specific growth substance, hopefully cast for the role of the cause of cancer, still eludes the research-workers.

Seven years before Leitch qualified in Glasgow, George Beatson, working at the Western Infirmary and at the Glasgow Cancer Hospital, had made a momentous clinical experiment based on a view of the nature and cause of cancer entirely opposed to the local parasitic theory which had so long occupied the minds of doctors. Beatson had long been interested in the effects of oophorectomy on lactation in animals and had done some experimental work. He reported that the first patient on whom he tried the practical application of his theories came to him with a letter from Dr. James W. Wallace, of Apsley Place, dated May 6, 1895. There are some discrepancies in the age and the dates of admission and operation between the records at what is now called the Royal Beatson Memorial Hospital and Beatson's published report; I have taken what follows from his own account (1896).

> The patient was 33 years old, with two children aged 3 years and 15 months. She had had a large mass in the breast with ulceration and outlying skin nodules which had rapidly recurred after a mastectomy, giving rise to infiltration throughout the scar area with ulceration. A piece of this recurrence was removed for biopsy and showed carcinoma. On June 15, 1895, Beatson did a bilateral oophorectomy and the tumour regressed during the following 8 months. It recurred again in 1897, but the patient was still alive in 1899, 4 years after the operation (Beatson 1899). In his paper in *The Lancet* in 1896 he had reported a second patient with a good initial response who had, however, died shortly afterwards.

This work was repeated and confirmed by other surgeons, and similar results were later produced by irradiation of the ovaries; but selection was indiscriminate, the number of women who responded was small, and the significance of the observation was missed for many years. Now, through work on neoplasms of some organs normally under hormone control in which Charles Huggins—a man in the great tradition of surgeons with inquiring minds—has played an outstanding part, the concept of hormone dependence in tumours has emerged. It has been clearly demonstrated that all malignant tumours are not necessarily autonomous or inevitably

* The Weild lecture for 1958, delivered before the Royal Faculty of Physicians and Surgeons, Glasgow, on Nov. 12.

self-perpetuating; also, that neoplastic cells may retain sufficient normal characteristics, even when they have metastasised, to function in the same way as those of their parent tissue. Aggressive neoplasms may still be capable of physiological control. They may even regress spontaneously under the influence of a normal change in hormone secretion, such as occurs when a natural menopause follows the development of a breast tumour (Smithers 1952).

Physiological control of disseminated neoplasms in man, for long periods, has now been seen sufficiently often by enough responsible people to be accepted as a fact—whereas in the past the same phenomenon, when observed by a few and called spontaneous regression, was not. As a result, cancer now seems to fall more easily into line with the normal growth of living things, which is naturally continuous by compound interest and which has to be controlled by many different mechanisms to form and maintain a complicated organism.

As ideas of hormone dependence became acceptable, as neoplasia appeared to be in line with normal development, and as tumours were seen to regress by the re-establishment of physiological control, a number of familiar clinical observations took on new significance. The progression of tumours from more benign to more aggressive states had long been observed clinically, but the ideas which dominated peoples' minds prevented them from drawing simple conclusions from the facts and forced them into devious explanations. Excellent work, largely by Foulds (1951, 1954, 1956) and Furth (1953, 1955), coming at a time of changing outlook, has given new life to the concept of independent progression of several growth characteristics in collections of neoplastic cells. This phenomenon of progression may depend on such things as selection of cells with increased survival value, adaptations to environment analogous to acquired drug resistance, and stimulation increasing with tumour size because induced by products derived from neighbouring cells. Such progressions in growth, taking place independently at greatly differing speeds as tissues pass on their way towards an autonomy they can never quite attain, and resulting in a wide variety of behaviour patterns, are now much more easily regarded as a reasonable explanation than was possible 30 years ago.

Emphasis has swung away from the old search for one specific growth substance responsible for a definable disease entity, towards an attempt to understand why cell populations in living organisms are so changeable that they may become independent of almost every known kind of stimulation and of inhibition. Dependency and autonomy are both seen to be relative and quantitative. Controlled development and uncontrolled growth appear to follow the blocking or unblocking of several synthesising systems in cells which may be influenced in a number of ways.

Instead of asking what chemical turns a normal cell into a cancer cell, much better questions are being formulated. What are the factors which in complex organisms transcend the cell, to unify and control a mass of protoplasm into orderly development and maintenance of a whole? What intracellular mechanisms of synthesis are chiefly concerned with growth and differentiation? In what ways do the interplay between these two, without which there is no life, become disturbed, so that tissue malformation occurs? What inherent mechanisms allow tissues once involved in this process to progress further and further away from dependence on normal organismic controls towards independent expression of their modified potentialities to form a new whole? To such questions as these we have a right one day to expect complicated but detailed answers in terms of organisation and its disturbance; to the question "What is the cause of cancer?" we have no right to expect any civil answer at all.

Isolation and Injury as Physiological Initiators of New Growth

If this view is more nearly correct than the old, then the causes of tissue malformation must be sought in the dynamic expression of the interaction between cells and their environment expressed in terms of disturbance of normal processes. We must go back to normal development and repair to find the mechanisms which become deranged in neoplasia. Starting with simple organisms which exhibit a number of controlled deviations from their paths of individual development, such as vegetative reproduction and regeneration, we see at once that these processes have much in common with neoplasia. Cell migration, dedifferentiation, and new growth occur in them all. The normal mechanisms controlling growth and differentiation are complicated and interrelated: they include local effects produced by one group of cells upon their neighbours, and general effects produced by hormones on competent cells wherever they may be in the body; they are also much concerned with nerve supply.

The common circumstances which set agamic reproduction and repair in motion are isolation and injury. Physical isolation of parts of some of the simpler organisms (hydra, for example) leads to the development of new wholes: when they are cut into pieces, each piece—if large enough—may grow into a whole new organism. The potential remains within the cells, the degree of organisation to be achieved is not too great, and the environment is favourable Physiological isolation may also initiate new growth and this too can be induced experimentally—by the isolation of the tip of the stolon with new hydranth formation in tubularia, for example (Child 1924). Physiological isolation is the means to agamic reproduction in some organisms when growth extends beyond the control of dominant regions—e.g., when the tail is shed to become a new whole in planaria (Child 1924). Given the chance of individual expression which follows isolation, all cells of fairly simple creatures may be able to reproduce a whole new organism: they merely require a suitable environment, but for agamic reproduction this will usually include enough cells of their own type.

In higher organisms the organisation needed for reproduction is too complex to be achieved except through the impetus of new chromosomal combination in a special environment. If a whole new organism is to result, isolation must occur at the very earliest stage. Although the capacity for vegetative reproduction is lost, local replacement of tissues is still possible in varying degrees. Injury is followed by repair which may range from complete regeneration of a limb to simple wound closure by scar tissue. Some power to regenerate is latent in almost all cells of every animal, but a complex organ composed of many tissues regenerates much less easily

than a single tissue where far less organisation is required. Regeneration of the liver can occur—rather as compensatory hypertrophy appears, for example, in one kidney when the other is removed. Replacement of a lost toe, however, is beyond the power of man. Lizards may remain able to regenerate their tails and the salamander retains into adult life its ability to regenerate a whole limb. The stages of regrowth are those of rapid cell division resembling embryonic development, with primitive cells dividing at first with the abandon of an anaplastic tumour but gradually slowing and differentiating, to be remodelled into a fully developed limb (Singer 1958). The process is most beautifully organised and the whole dependent on an adequate nerve supply. So long as the necessary threshold number of nerve fibres is available, it does not seem to matter if they are sensory or motor. The tadpole has good regnerative powers, but when it becomes an adult frog it normally loses the ability to grow new limbs. A frog's arm can, however, be made to regenerate if the nerve supply from a leg is deflected to supplement that of the forelimb stump (Singer 1958).

Injury, like isolation, initiates new growth, and repeated injury may profoundly alter the processes both of agamic reproduction and of regeneration. New hydranths can be made to grow in corymorpha by trauma, and—of particular interest—the amount of trauma required varies with the distance at which it is applied from the dominant region (Huxley and de Beer 1934). In other words, the amount of stimulus needed to produce this new growth depends on the strength of the forces of organisation or the competition for food supply which have to be overcome. Regeneration of frogs' limbs may be produced not only by providing an increased nerve supply but also by repeated injury to the amputation stump. The regrowth which occurs after repeated trauma is not well organised; it tends to be irregular in structure and imperfectly modelled and can be prevented altogether by denervation.

Isolation and injury initiate new growth. Organisation shapes it. An adequate nerve supply is required for control and remodelling. Increasing the nerve supply makes more complicated tissue organisation possible. Repeating the injury makes more growth possible. A decline either in nerve supply or in tissue responsiveness to nervous stimulation makes new growth less well organised. The interplay throughout is between cell potential and environmental restraint.

Isolation and Injury as Factors in Tumour Production

The gradual approach to disorganised neoplasia with which these physiological processes merge is obvious. In higher organisms physiological isolation of parts, and repeated injuries or similar stimulations, can initiate new growth. This may then proceed under favourable circumstances towards independent expression of the potentialities which remain to the cells concerned.

There has lately been remarkable experimental evidence of such induction of neoplasms through tissue isolation.

Oppenheimer, Oppenheimer, and Stout in 1948 induced sarcomas by chance when wrapping rats' kidneys in 'Cellophane' in an attempt to produce hypertension. Turner (1941) had previously induced such tumours by embedding discs of 'Bakelite'. The nature of the carcinogenic agent seemed quite obscure to them then.

Now, Oppenheimer, Stout, Oppenheimer, Danishefsky, and Willhite (1958) have produced tumours in rodents by embedding plastic films, metal foils, keratin sheets, parchment, paper, silk, glass, mica, tin, and other substances. In powdered form—when they should be chemically more reactive—or in sponge or fine mesh when the barrier is incomplete, these substances produce few tumours; the physical form, not the chemical structure, has been shown to be all-important in this action. The embedded material becomes enveloped on one side by a connective tissue pocket, where high fibroblastic activity at first occurs and in which progress to anaplasia and sarcoma formation may follow. Removal of the film six months or more after embedding does not affect tumour production if the pocket is left intact; but if the pocket is removed or exposed, no tumours develop. The neoplasia occurs only in the isolated pocket and only if given sufficient time; removal of the pocket in which the change is taking place removes the tumour risk, but—of much more interest—removal of the pocket from isolation, without its removal from the body, also removes the tumour risk.

On the clinical side, repeated demands for healing have long been known to be associated with tumour production; the development of neoplasms at the edge of chronic ulcers is a commonplace, and there are numerous examples of tumours resulting from continued irritation. Repeated trauma has its physiological counterpart in constant hormone stimulation. Circulating hormones reach all tissues but affect only those which are competent to respond to their particular stimulus. Abnormalities leading to prolonged hormone stimulation act by keeping up the demand for function, and may also initiate new growth, which is for a time dependent on that stimulus—as another great inquiring surgeon, Sir Thomas Dunhill (1937), demonstrated, in a piece of work which is surely of equal historic importance to that of Sir George Beatson, when he reported hormone dependent carcinoma of the thyroid and its control with thyroxine.

The concept of neoplasia which is emerging turns out to be only an extension of one of which Ribbert was an advocate (1895). The process is seen in terms of cells with varying potentials for regeneration, normally controlled within an organismic pattern from which they may be released either by isolation from that control or by repeated demands for function which raise their growth capacity above that of the controls being exercised. The whole pattern is in keeping with normal growth and development, but is extended by the inherent tendency of cell groups to progress in growth habit towards autonomy by self-expression whenever they are given the chance.

Clinical Observation of Neoplastic Disease

In clinical cancer work we are dealing with a variety of abnormalities of growth and differentiation, due either to inherited defects or to abnormal environments and manifest as changes in amount of growth, degree of differentiation, and in tissue position or blending. We are concerned with transmissible defects such as those leading to retinoblastoma, intestinal polyposis, or xeroderma pigmentosum; and also with acquired malformations such as those of tissue arrest during development leading to nephroblastoma, of displacement leading to melanoma, of blending leading to hamartoma, and of over stimulation from without, leading, for example, to skin tumours, or from within, leading (in different ways) to bladder tumours or to tumours of the thyroid.

These are presented to us through the many people who suffer from them in a bewildering variety of graded

manifestations. Hyperplasia blends imperceptibly into neoplasia. Innocence and malignancy are no more than convenient terms of relative prognostic value. Malformations resulting in tumours such, for example, as accessory adrenal glands or angiomas are neoplasms without dedifferentiation; fibromas and adenomas are disorganised, somewhat dedifferentiated neoplasms without invasion. Epithelium may infiltrate at the edge of healing ulcers with or without forming neoplasms; epithelial sinuses (Rokitansky-Aschoff) may penetrate the muscular layer in the wall of the gallbladder and exist and in the subserous layer without being malignant. Bone-marrow embolism has been recognised for many years; even white matter from the brain has been found in the lung after trauma (Krakower 1936). Normal tissue cells may be carried in blood-vessels or lymphatics, with or without the formation of non-malignant metastases (Balme 1954, Smithers 1959). Benign tumours may give rise to benign, fully functioning metastases (King and Wood 1950), malignant tumours may give rise to benign metastases, benign tumours may possibly give rise to malignant metastases. We talk in curious mixed terms of carcinomas "in situ", of pre-invasive cancer, of malignant adenomas, of benign metastasising tumours, and even of non-lethal cancer morphologically indistinguishable from the lethal form. We persist in trying to exclude those observations which do not fit in with our outmoded view of cancer as a sharply defined disease entity, by providing them with convenient labels.

These verbal acrobatics alone should long ago have led us to regard the basic theory with the utmost suspicion. The whole gamut of abnormality of growth, progressing and regressing, is involved. The wonder is that, in the turmoil of growth, development, repair, and maintenance which goes on continuously in all living creatures, we retain a recognisable and functioning form at all—not that tissue malformations and disorganisations sometimes occur. By merely moving the point of diagnosis on our scale of growth disorder we can make this word "cancer" represent a more and more serious disease, until by definition it is always fatal. By shifting our ground in the other direction we can produce figures to show that our treatments are continually improving. This game of tug-of-war has become a popular sport between some pathologists and surgeons.

All the many definitions of cancer that have been put forward have dealt with the behaviour of cell groups in the living organism in terms of deviations from normal patterns, none of which are peculiar to cancer. Our definitions have long been ahead of our beliefs. What constitutes human cancer as accepted by the Registrar General in his reports, has always been the presence of these deviations in behaviour in sufficient number and degree to have been acceptable to one particular doctor signing the death certificate. In extreme forms no one has any doubt about classification; when the patient dies there is seldom much argument. In borderline forms the diagnosis remains a matter of opinion. There is controversy about what label is to be attached because the behaviour patterns merge imperceptibly into changes which would not be called cancerous by anyone. It should, in fact, have been clear enough to doctors all these years that they were not dealing with a specific disease but with one end of a scale of changes in several tissue behaviour patterns from which they have arbitrarily singled out cases which demonstrate enough deviation from the normal to have made them feel individually justified in giving these variants collectively a single name.

It should be clear enough to those who observe the clinical scene that the study of the pathogenesis of cancer must be concerned with deviations from the normal in every behaviour pattern of growth and development which may lead to tissue malformation on a graduated scale of heteroplasia, metaplasia, hyperplasia, neoplasia, migration, invasion, and metastasis. The persistent use of this ill-defined word "cancer", as though it represented a specific disease instead of a composite facet of tissue malformation, is misleading and unscientific. "Cancer" is to the neoplastic disorders what "galloping consumption" used to be to the infections—it is merely less precise. The next generation may well wonder how we came to retain this term for so long in our medical journals when the Victorians managed to confine their own particular, terrifying, end-of-scale bogy to their novels.

Public and Professional Response to the Changing Outlook

The change in outlook which has taken place over the past thirty years has as yet made hardly any impact on the general public. It seems at times to have made only a small impression on general medical thought, even though it has already produced a profound change in specialised practice.

The more curious concepts of cancer which still dominate lay thinking and infect portions of the medical profession are, of course, not medical and biological in origin but philosophical and psychological. They are to do with that part of our natures which leads us to adopt one set of views rather than another. They are concerned with choice and meaning, with selection of information to fit preconceived notions and with interpretations based on personal bias. The public view of the pathogenesis of cancer is quite unreal, being governed by fear and hope instead of by knowledge and understanding. This view is supported by both of the two chief forms of publicity about cancer—that all too prominent section of the Press which seeks sensation, and those common requests for money which either use fear or the promise of a simple solution as the basis for their appeal. A few serious attempts at public education have made a slight impression in selected populations. They have shaken the belief—which, in fact, depends on definition—that cancer is inevitably fatal, and have persuaded a few to seek early advice because they were led to understand—which is not true in every case—that treatment given soon after the first symptom can effect a cure. Little real effort has ever been made to promote public understanding of the kind of problem with which we are really dealing, and continued statements about one day discovering both the cause and the cure of a terrible disease called cancer only help to keep people ignorant of what is known and misled about what is possible.

The medical profession, which in this matter as in many others is only a rather special category within the general public, is too often infected with the same ideas, influenced by its own propaganda and biased by its own aspirations. Our journals erupt in frequent statements about cancer education and cancer diagnosis, cancer

cause, and cancer cure; about the answer which is just around the corner and the chemotherapy which will solve all problems. These are the muddles and the myths which we create for ourselves.

Political differences would be unlikely to disappear if only we were to agree on a definition of democracy; if our international differences were to vanish, however, we should then have little trouble with the definitions of any words we chose to embrace our political systems. Linguistic analysis will not solve our difficulties but it may help us to see more clearly what our problems really are. With broad philosophical questions such as " What is freedom ?" or " What is consciousness ?" definitions help us little—even when we can get them. The same is true of broad biological questions such as " What is life ?" and even " What is cancer ?" We need what A. J. Ayer (1955) has called " A detailed account of the work which the concept has to do, a critical investigation of the territory which it is supposed to cover ". The territory with which we are concerned when we speak of cancer is contained within that of tissue malformation. The processes involved are those of disorganisation of growth and differentiation. The degree of variation from the normal behaviour patterns changes continuously along a scale, with a tendency for independent progression of each characteristic towards complete escape from control. The word cancer vaguely covers the most disorganised of these tissue malformations, being applied according to individual preference on the basis of a selection of those degrees of change in several characteristics which are expected to give rise to the greatest danger to the life of the organism. Since it can have no precise boundaries this side death, it would be better if we were to abandon its use in communications having some pretence to scientific reporting.

Had I such pretensions, the title of this lecture would have been boldly proclaimed as On the Pathogenesis of Tissue Malformation. It is a subject worthy of our greatest biologists and a challenge which we, as doctors, are eager to see grandly met from the whole man right down to the molecular level. As the territory becomes more clearly mapped, the time when this standard may be expected from a Weild lecturer must surely be drawing nearer.

REFERENCES

Ayer, A. J. (1955) Studies in Communication; p. 11. London.
Balme, H. W. (1954) *Lancet*, i, 812.
Beatson, G. T. (1896) *ibid.* ii, 104, 162.
— (1899) *Brit. med. J.* i, 442.
Child, C. M. (1924) Physiological Foundations of Behavior; pp. 152, 154, 155. New York.
Dunhill, T. (1937) *Trans. med. Soc. Lond.* **60**, 234.
Foulds, L. (1951) *Ann. R. Coll. Surg. Engl.* **9**, 93.
— (1954) *Cancer Res.* **14**, 327.
— (1956) *J. nat. Cancer Inst.* **17** ,701.
Furth, J. (1953) *Cancer Res.* **13**, 477.
— (1955) *Recent Progr. Hormone Res.* **11**, 221.
Huxley, J. S., de Beer, G. R. (1934) Elements of Experimental Embryology; p. 290. London.
King, E. S. J., Wood, B. (1950) *J. Path. Bact.* **62**, 29.
Krakower, C. (1936) *Arch. Path.* **22**, 113.
Leitch, A. (1928) Proceedings of the International Cancer Conference (British Empire Cancer Campaign), London, 1928; p. 20. Bristol.
Oppenheimer, B. S., Oppenheimer, E. T., Stout, A. P. (1948) *Proc. Soc. exp. Biol., N.Y.* **67**, 33.
— Stout, A. P., Oppenheimer, E. T., Danishefsky, X., Willhite, M. (1958) Scientific exhibit no. 8 at Seventh International Cancer Congress, London.
Ribbert, H. (1895) *Virchows Arch.* **141**, 153.
Singer, M. (1958) *Sci. American*, **199**, 79.
Smithers, D. W. (1952) *J. Fac. Radiologists*, **4**, 89.
— (1959) *ibid.* **10**, 3.
Turner, F. C. (1941) *J. nat. Cancer Inst.* **2**, 81.

GAS-ANALYTICAL STUDIES IN SEVERE PNEUMONIA

OBSERVATIONS DURING THE 1957 INFLUENZA EPIDEMIC

HEINRICH HERZOG, M.D. Zürich
HANS STAUB, M.D. Zürich
ROLAND RICHTERICH, M.D. Basle
From the Medical University Clinic, Basle, Switzerland

BETWEEN September and December, 1957, 264 patients with severe Asian influenza were admitted to the University Hospital (Bürgerspital), Basle. 125 suffered from chest complications—tracheobronchitis, bronchopneumonia, or pleuropneumonia—and, though in most cases the respiratory illness proved amenable to routine treatment, 22 needed special therapeutic measures, such as tracheotomy and artificial respiration. 12 of these 22 died.

We report our experience because we feel that current treatment has room for improvement. We were able, moreover, to follow the course of many of the severe cases by gas-analytical studies; and our findings may be applicable to other types of fulminating pulmonary infection. Preliminary reports have already been published (Bernstein 1958, Herzog 1958, Reber 1958, Staub 1958, Stricker 1958).

Clinical Observations

10 of the 22 unselected patients on whom we performed gas-analytical studies gave a history of previous cardiac or pulmonary illness. 6 of them survived, in contrast to only 4 survivors among the 12 patients with a negative cardiopulmonary history. This suggests that patients with chronic heart or lung disease may have an increased resistance to acute pulmonary infections. Perhaps because of pre-existing right ventricular hypertrophy, their cardiovascular system may be better adapted to episodes of pulmonary hypertension.

It was remarkable that most of the patients who died had been ill for only two to four days before admission; but this kind of fulminating course has been observed by others (Public Health Laboratory Service 1958). The usual presenting signs were fever, cyanosis, and dyspnœa. 6 patients were admitted in a state of cardiovascular collapse (systolic pressure below 80 mm. Hg), 2 in hypoxic coma, 1 with left ventricular failure, and 1 with meningism. All the 6 who had cardiovascular failure died within four days of admission, despite treatment with plasma, pressor drugs (' Arterenol '), corticoids, and blood, in addition to routine measures. Irreversible cardiovascular collapse was thus the direct cause of death in cases 2, 8, 14 and 17 (table I); and it was a contributory cause in cases 1, 5, 9, and 21. No organic explanation for it could be found at necropsy. Congestive heart-failure was diagnosed, and may have been the main cause of death, in 4 patients; pulmonary œdema was the presenting syndrome in both patients who suffered from mitral disease; hypoxic coma was seen in a case with mitral and aortic disease and in a case with chronic bronchitis and kyphoscoliosis. 1 patient showed all the clinical signs of meningitis but had a normal cerebrospinal fluid: this is seen in 2–12% of patients with pneumonia, particularly in young males with upper-lobe involvement (Dupré 1895, Goldfield and Weinstein 1952).

Laboratory Findings

In the survivors the white-cell count showed a polymorphonuclear leucocytosis. 6 patients who had a

white-cell count of less than 5000 per c.mm. all died.

The white cells in the fatal cases were predominantly neutrophils, showing a shift to the left (49% stab-cells in case 9). Marrow puncture in case 14 revealed hypoplasia and maturation arrest of the granulocytes. The cause of this is not known; but we should mention that 2 of the 6 fatal cases had received an amidopyrine derivative (' Irgapyrin '). Of these 2 patients, 1 had thrombocytopenia as well.

TABLE I—DETAILS OF PATIENTS STUDIED

No.	Age and sex	Previous cardiac or pulmonary disease	Days of illness before admission	Presenting features	Outcome
1	58 M	Mitral disease	7	Pulmonary œdema, collapse, cyanosis	Death 24 hours after admission: hypoxia, congestive heart-failure, collapse, leucopenia
2	56 M	..	3	Collapse, fever, cyanosis, dyspnœa	Death on 3rd day: collapse, hypoxia, leucopenia
3	44 M	Emphysema	4	Fever, cyanosis	Death on 4th day: respiratory failure
4	49 F	Bronchitis	3	Fever, cyanosis, dyspnœa	Death on 6th day: hypoxia
5	69 F	..	10	Collapse, fever, cyanosis, dyspnœa	Death on 4th day: collapse and intestinal hæmorrhage
6	37 M	Mitral and aortic disease	16 hours	Stupor, fever, cyanosis, dyspnœa	Death 8 hours after admission: hypoxia and congestive heart-failure
7	59 M	Asthma	6	Fever, dyspnœa, cyanosis	Recovery
8	42 M	..	7	Fever, dyspnœa	Death on 3rd day: collapse, hypoxia, leucopenia
9	73 M	..	7	Collapse, fever, cyanosis	Death on 2nd day: collapse and congestive heart-failure
10	56 M	Mitral disease	5	Fever, cyanosis, dyspnœa	Recovery
11	27 F	..	3	Fever, stridor, cyanosis, dyspnœa	Recovery
12	37 F	Mitral disease	7	Pulmonary œdema, cyanosis, dyspnœa	Recovery
13	56 M	Bronchitis, kypho-scoliosis	10	Coma, fever, cyanosis, collapse	Recovery
14	17 M	..	2	Meningism, fever, pulmonary œdema	Death on 2nd day: collapse, leucopenia
15	60 M	Emphysema	10	Fever, cyanosis, dyspnœa	Recovery
16	54 M	..	2	Cyanosis, dyspnœa	Recovery
17	22 M	..	2	Collapse, fever, cyanosis	Death on 3rd day: collapse
18	72 M	..	6	Fever, cyanosis, dyspnœa	Death on 4th day: congestive heart-failure, leucopenia
19	65 M	Bronchitis	5	Fever, cyanosis, dyspnœa	Recovery
20	49 M	..	8	Cyanosis, dyspnœa	Recovery
21	55 F	..	5	Fever, cyanosis	Death on 2nd day: collapse
22	20 M	..	12	Fever, cyanosis, dyspnœa	Recovery

TABLE II—GAS-ANALYTICAL FINDINGS IN ARTERIAL BLOOD

No.	Respiring air			Respiring air + 30–50% oxygen		
	O_2 saturation (%)	pCO_2 (mm. Hg)	pH	O_2 saturation (%)	pCO_2 (mm. Hg)	pH
1 f	..	..	..	36·7	48·7	7·24
2 f	..	..	..	38·1	50·5	7·38
3 f	40·1	54·4	7·40	91·6	61·5	7·35
4 f	..	..	..	43·7	53·4	7·30
5 f	45·5	86·0	7·25	88·0	92·7	7·22
6 f	..	..	..	47·8	27·9	7·44
7	59·4	60·4	7·36	97·8	63·2	7·34
8 f	..	..	..	61·4	35·7	7·44
9 f	64·1	25·7	7·43	74·0	26·8	7·42
10	65·9	38·1	7·49	88·2	36·5	7·48
11	66·2	..	7·48	82·8	39·1	7·48
12	..	..	..	66·3	40·1	7·30
13	..	..	..	73·6	65·3	7·21
14 f	..	..	..	76·5	30·2	7·48
15	77·4	38·6	7·49	86·3	42·2	7·45
16	78·3	50·7	7·37	93·6	53·2	7·35
17 f	81·2	29·5	7·49	87·5	28·0	7·49
18 f	83·0	31·0	7·38	89·5	31·5	7·37
19	84·2	37·8	7·46	91·4	42·1	7·44
20	86·7	29·0	7·50	95·4	28·3	7·51
21 f	..	..	..	90·8	30·1	7·37
22	94·1	..	..	95·8	32·6	7·47
Normal values	95–97	40·0	7·38–7·41	100	40·0	7·38–7·41

f, fatal outcome.

Most patients were dehydrated, and 2 had a raised blood-urea, on admission. Agammaglobulinæmia was excluded in 4 of the 12 patients who died.

A rise in the alpha-globulins and a slight depression in the gamma-globulins was noted; and 3 of the 4 patients examined had a high plasma-fibrinogen. Such findings are said to be usual in pneumonia (Bodansky and Bodansky 1952).

Bacteriological studies of sputum or tracheal aspirate showed coagulase-positive staphylococci in 10 patients (three strains resistant to penicillin and one to tetracycline); coliforms in 2; β-hæmolytic streptococci in 4; and non-hæmolytic streptococci in 2. In case 9 the blood-culture grew pneumococci.

Postmortem Findings

Necropsy records were available in 11 cases. As stated by Werthemann (1958), the main pulmonary features were extensive alveolar and interstitial hæmorrhagic and purulent inflammation, complicated in some cases by exudative pleurisy. Very striking and characteristic was the severe tracheobronchitis, often hæmorrhagic and pseudomembranous.

4 subjects also showed fresh superficial erosions of the gastric and duodenal mucosa, similar to " stress " ulcers. Only 2 of them had received corticoids (prednisone). Subendocardial hæmorrhages were found in 2 cases; and 1 had cerebral purpura.

Gas-analytical Studies

Methods

Blood for gas-analysis was obtained by puncture of the brachial artery.

Oxygen (O_2) saturation was measured by Courtice's modification of Haldane's method (Courtice and Douglas 1947). Arterial carbon-dioxide (CO_2) content was determined manometrically (Van Slyke 1922). The arterial pH was measured on a ' Metrohm ' pH-meter (accuracy $\pm 0{\cdot}02$ units). The CO_2 tension (pCO_2) was calculated from the CO_2 saturation and the pH, using the Hasselbalch-Henderson formula corrected for temperature. In some patients alveolar CO_2 concentration was measured simultaneously using Fowler's (1948) infra-red method, Liston-Becker apparatus, and the pCO_2.

O_2 Saturation

Hypoxia was present on admission in all patients. After receiving oxygen, O_2 saturation rose but it reached normal values in only 3 patients (table II). The lowest O_2 saturations were 36·7%, 38·1%, and 43·7% (in spite of continuous oxygen administration). There was a close correlation between the degree of hypoxia and survival. Of 10 patients with O_2 saturation of less than 80% during oxygen administration, only 2 survived: both had had chronic rheumatic heart-disease and chronic bronchitis. It is noteworthy that even those patients who had O_2 saturations of less than 60% survived up to six days without developing signs of irreversible damage to vital organs; and most of them were conscious up to the last

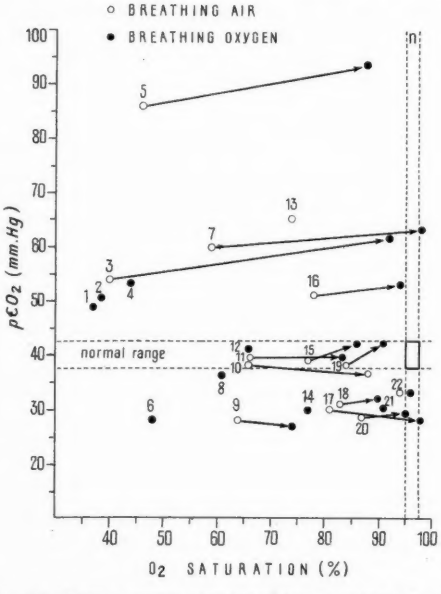


Fig. 1—The effect of oxygen administration on arterial O_2 saturation and pCO_2.

few hours. Repeated electrocardiograms showed no localised or generalised cardiac ischæmia, nor did we see the signs of renal failure described by Black and Stanbury (1958). This shows that, even when severe hypoxia continues for a long time, everything should be tried to tide the patient over the crisis.

The typical gas-analytical feature of pneumonia is hypoxia in the presence of normal, depressed, or even elevated carbon-dioxide tension.

The most important cause is the disturbed ventilation/perfusion ratio—i.e., the imperfect distribution of blood and air in the lungs. Perfusion of non-ventilated alveoli leads to massive venous admixture, and this is directly responsible for the hypoxia. (About a third of the mixed venous blood has to be short-circuited to produce the observed changes.) In such cases —with massive arteriovenous short-circuits around poorly ventilated or non-ventilated alveoli—oxygen inhalation does not raise arterial O_2 saturation to 100% as it does in normal people; elevation of the alveolar pO_2 cannot affect shunted blood. Thus, the effect of inhaled oxygen on arterial O_2 saturation is a qualitative test of venous admixture (Rossier and Wiesinger 1948). In chronic pulmonary disease with transient hypoxia this mechanism loses its significance, since there is time for the development of adaptive reflexes which diminish the perfusion of non-ventilated alveoli (Euler and Liljestrand 1946).

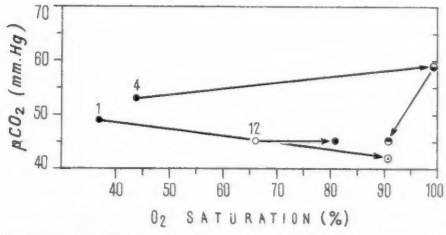


Fig. 2—The effect of various therapeutic measures on arterial O_2 saturation and pCO_2. Case 1 before and after tracheotomy. Case 4 after tracheotomy, after artificial respiration, and after isoprenaline and trypsin inhalation. Case 12 before and after artificial respiration.

The second cause of hypoxia in pneumonia is the disturbed pulmonary O_2-diffusion capacity, due to reduction of the alveolar (capillary) surface, and to the congestion and infiltration of the remaining membranes.

The third and least important cause is the shift to the right of the oxyhæmoglobin-dissociation curve, brought about by the rise in body temperature, the elevated CO_2 tension, and the acidosis.

CO_2 Tension

The pCO_2 followed one of two patterns. Usually it was normal or slightly depressed—probably as a sequel to alveolar hyperventilation—but occasionally it was raised.

Most patients with CO_2 retention gave a history of chronic bronchial obstruction (table I): in these cases oxygen administration tends to aggravate CO_2 retention since the patient's respiration is regulated by O_2-sensitive, not by CO_2-sensitive, receptors (fig. 1).

The pattern of arterial pH varied under several competing influences. The hyperventilation, shown by the lowering of the pCO_2, led us to expect a mild alkalosis; and this was in fact the common finding (table II). Some patients, however, had severe acidosis: and, in view of the low pCO_2, one must assume that under hypoxia they had developed alternative metabolic pathways leading to a metabolic acidosis.

In some patients the pCO_2 was determined simultaneously in the alveolar air by the infra-red method and

TABLE III—ARTERIOALVEOLAR pCO_2 GRADIENT

No.	Date and time	O_2 saturation (%)	Arterial pCO_2 (mm. Hg)	Alveolar pCO_2 (mm. Hg)	pCO_2 gradient (mm. Hg)	Respiration
1	Nov. 24, 2.30 P.M.	36·7	48·7	37·2	11·5	A/O_2
	4.00 P.M.	90·7	41·8	35·5	6·3	E—A/O_2: 12 l/min.
5	Dec. 13, 6.00 P.M.	89·1	66·6	42·7	23·9	E—A/O_2: 10 l/min.
	„ 14, 2.00 P.M.	91·5	65·6	40·6	25·0	E—A/O_2: 10 l/min.
8	„ 12, 4.00 P.M.	75·4	41·4	36·3	6·1	A
	„ 13, 2.00 P.M.	69·3	41·0	35·7	5·3	A
13	„ 13, 1.00 P.M.	79·1	48·6	32·8	15·8	E—A/O_2: 9 l/min.
	„ 18, 10.00 A.M.	74·3	39·2	33·5	5·7	A
	10.00 A.M.	91·6	44·7	34·2	10·5	A/O_2
19	Nov. 28	84·2	37·8	31·4	6·4	A
	Dec. 18	88·2	41·3	37·8	3·5	A
15	„ 13	77·4	38·6	32·0	6·8	A
22	„ 18	95·8	32·6	31·4	1·2	A/O_2
	Normal values	95–97	40·0	39·1 ± 1·8	0·9 ± 1·8	..

A, room air. O_2, 30–50% oxygen. E, Engström respirator.

in the arterial blood by calculations based on pH and CO_2 content (table III). The two values can differ considerably, the tension gradient in some cases being more than 20 mm. Hg. Such a gradient has previously been observed in patients with chronic pulmonary disease (Bitter and Rahn 1956, Severinghaus and Stupfel 1957) and in normal subjects under experimental conditions—blockage of a pulmonary artery (Bitter and Rahn 1956, Scherrer and Hodler 1957). In acute pulmonary infections it assumes importance when artificial respiration is regulated by the alveolar instead of the arterial pCO_2.

The development of a gradient in the pCO_2 between arterial blood and alveolar air may be explained as follows. Inspiration fills poorly perfused alveoli with dead-space air which contains only small amounts of CO_2. In expiration this air mixes with air from normally ventilated and perfused alveoli whose pCO_2 is the same as that of arterial blood. Thus an alveolar dead space is created by non-perfused alveoli.

A gradient in the pCO_2 between arterial blood and alveolar air is therefore a sign of uneven alveolar perfusion.

Effect of Treatment

Oxygen has been used extensively to combat hypoxia since Stadie (1922) first demonstrated its beneficial effects. The O_2 saturation rose in all but 5 of our patients above 65% (table II). These 5, whose O_2 saturation stayed below 65%, all died: they were the only ones in whom hypoxia may have contributed to the fatal outcome. In 12 patients, as soon as respiratory insufficiency due to bronchial obstruction was suspected, tracheotomy was performed. Only 3 of these survived.

Immediately after tracheotomy, and at suitable intervals thereafter, secretions were aspirated with a suction pump and bronchial catheters from the bronchi. The remarkable effect of this simple measure is evident from fig. 2. Patients with a history or clinical evidence of bronchospasm received aerosol isopropylnoradrenaline and/or theophylline-ethylene-diamine by intravenous injections.

If O_2 unsaturation persisted, with or without CO_2 retention, artificial respiration (using an Engström apparatus) was begun.

Fig. 2 shows the rise in O_2 saturation from 43·7% after tracheotomy and endobronchial suction to 100% after artificial respiration, and the subsequent fall in pCO_2 from 59 to 45 mm. Hg after inhalation of trypsin and isoprenaline ('Aleudrin') by aerosol. In another patient O_2 saturation rose from 36·7 to 90·7% after artificial respiration. Artificial respiration was regulated not only by direct infra-red analysis of the alveolar CO_2 but also by checks on the arterial pCO_2.

Discussion

In 1919 Stadie in a now classical paper reported on the arterial O_2 unsaturation in 33 patients with post-influenzal pneumonia. In his series only 1 patient with O_2 saturation of less than 75% survived, whereas in our series 5 of 22 lived. The mean arterial O_2 saturation of Stadie's 16 fatal cases was 63% and of his surviving patients 81%. In our series the corresponding figures were 59% and 75%. Though this is an improvement, even more might have been expected considering that Stadie had no antibiotics, arterenol, corticoids, or respirators at his disposal.

The main causes of death in our 12 cases were as follows:

Hypoxia, cardiovascular collapse, congestive heart-failure, leucopenia (case 1).
Hypoxia, collapse, leucopenia (cases 2, 8).
Collapse, leucopenia (cases 14, 17).
Hypoxia (case 4).
Collapse, intestinal hæmorrhage (case 5).
Collapse (case 21).
Hypoxia, congestive heart-failure (case 6).
Collapse, congestive heart-failure (case 9).
Congestive heart-failure, leucopenia (case 18).

Hypoxia was thus directly responsible for 1 death only; and it may have been a contributory cause in another 4. This suggests that patients with severe but adequately treated acute pulmonary infection no longer die from respiratory failure but from other causes. Hypoxia may, in fact, be considerably less important than has been thought. Huckabee (1958) recently showed that tissue hypoxia has to be feared only if arterial O_2 saturation falls below 60–75%.

Congestive heart-failure was a significant cause of death in 4 cases. These patients will remain poor risks even though they are likely to survive acute episodes of pulmonary hypertension.

Irreversible cardiovascular collapse, seen in 8 cases, was without doubt the most important single cause of death. The fact that 6 of the 8 patients also had leucopenia leads us to suspect a common causal factor—perhaps a toxin of bacterial origin. We feel that the outlook of these patients could be improved if the following measures were taken:

1. No potential bone-marrow depressants, such as amido-pyrine derivatives, should be used, either as "prophylactics" for influenza or as antipyretics.

2. Fever should be treated by physical means supplemented by innocuous antipyretics such as aspirin. Rapid temperature changes must be avoided, however, since they tend to produce hypotension and cardiovascular collapse. Perhaps it would be useful to induce hypothermia in these patients, but we still do not know enough to justify such drastic therapy.

3. Unless contraindicated (e.g., by congestive failure) fresh whole-blood transfusions should be given. In special circumstances the transfusion of fresh leucocytes may have to be considered.

4. It may well be that such epidemics are a trap for patients with agammaglobulinæmia. Since it is hardly possible, however, to estimate the gamma-globulins in all patients during epidemics, routine use of gamma-globulin seems justified.

5. Bacterial or viral toxins cannot be removed at present and it seems improbable that such large molecular substances could be eliminated by dialysis. Nevertheless, exchange transfusions might be worth trying in desperate cases with the dual purpose of removing toxic substances and correcting the leucopenia.

The recent epidemic has demonstrated the considerable advances in the treatment of respiratory failure. Most of the patients who died did not succumb to hypoxia. Nevertheless, the toll was still too high; and only by better management can we hope to reduce it.

Summary

Of 125 patients suffering from Asian influenza with pulmonary complications, 22 were dangerously ill and 11 died. The clinical, bacteriological, and gas-analytical features of these 22 cases are presented.

In many cases an arterioalveolar pCO_2 gradient was observed.

Hypoxia from respiratory failure was responsible for the fatal outcome in 2 patients only. Some patients suffered from severe long-continued hypoxia without developing signs of damage to brain, heart, or kidney.

The most important cause of death was irreversible cardiovascular collapse, often associated with leucopenia.

The therapeutic implications of these findings are discussed.

References at foot of next column

TRACHEOTOMY IN ACUTE RESPIRATORY DISEASE

LINDSAY A. G. DAVIDSON
M.B. Edin., M.R.C.P., M.R.C.P.E.
SENIOR REGISTRAR, UNITED BIRMINGHAM HOSPITALS, AND RESEARCH FELLOW, UNIVERSITY OF BIRMINGHAM

From the Department of Medicine, Queen Elizabeth Hospital

TRACHEOTOMY has been performed for over two thousand years to relieve laryngeal obstruction (Priest 1952); but only in the last decade has it been seen to have a wide application in the prevention and treatment of obstruction of the trachea and bronchi. Such obstruction is most often caused by accumulation of bronchial and pulmonary secretions at a time when the cough mechanism is lost or depressed—e.g., after operations, when it is the main cause of collapse of the lung (Haight and Ranson 1941, Williams 1951); in poliomyelitis (Lassen 1953, Blair 1955, Sandiford 1957); after head injuries (Echols et al. 1950, Maciver et al. 1958); and in barbiturate poisoning (Lewy and Sibbitt 1951, Blair 1955, Walford et al. 1955).

Sputum retention can also present a problem in several groups of primary respiratory diseases.

1. The largest group consists of patients with chronic bronchitis and emphysema (moderate or severe) who develop an acute attack of bronchitis or bronchopneumonia. This group is not restricted to respiratory cripples: indeed, patients with chronic emphysema and cor pulmonale but without copious sputum do not often benefit from tracheotomy, the value of which lies in the relief of sputum-induced obstruction.

2. The second group comprises patients—often elderly—who are exhausted by their illness or by continued coughing, and can no longer make the effort required to raise viscid sputum.

3. In some patients coughing is inhibited by severe pleuritic or other pain.

4. Finally, in patients belonging to any of these three groups the respiratory centre and cough mechanism may have been further depressed by sedation.

In all these patients it is the depression of the cough mechanism, resulting in retention of sputum which initiates the train of events leading to asphyxia. In the large majority incipient obstruction can be relieved by simple encouragement and supervised posturing and coughing. A few, however, do not respond to such simple measures: they require direct aspiration if asphyxia is not to progress to an irreversible stage. This stage can be reached in less than an hour.

DR. HERZOG AND OTHERS: REFERENCES

Bernstein, A. (1958) *Praxis*, **47**, 135.
Bitter, H. S., Rahn, H. (1956) Studies in Respiratory Physiology; p. 466. Wright Air Development Center Technical Report. M. (1957).
Black, D. A. K., Stanbury, S. W. (1958) *Brit. med. J.* i, 872.
Bodansky, M., Bodansky, O. (1952) Biochemistry of Disease. New York.
Courtice, F. C., Douglas, C. G. (1947) *J. Physiol.* **105**, 345.
Dupré, E. (1895) *Congr. franç. Méd.* **1**, 411.
Euler, U. S. von, Liljestrand, G. (1946) *Acta physiol. scand.* **12**, 301.
Fowler, R. C. (1948) *Amer. J. Physiol.* **155**, 436.
Goldfield, M., Weinstein, L. (1958) *Boston med. Quart.* **3**, 70.
Herzog, H. (1958) *Praxis*, **47**, 140.
Huckabee, W. E. (1958) *J. clin. Invest.* **37**, 264.
Public Health Laboratory Service (1958) *Brit. med. J.* i, 915.
Reber, H. (1958) *Praxis*, **47**, 147.
Rossier, P. H., Wiesinger, K. (1948) *Beitr. Klin. Tuberk.* **101**, 407.
Scherrer, M., Hodler, J. (1957) *Schweiz. med. Wschr.* **87**, 1509.
Severinghaus, H. W., Stupfel, M. (1957) *J. appl. Physiol.* **10**, 335.
Stadie, W. C. (1919) *J. exp. Med.* **30**, 215.
— (1922) *ibid.* **35**, 337.
Staub, H. (1958) *Praxis*, **47**, 132.
Stricker, E. (1958) *ibid.* p. 138.
Van Slyke, D. D. (1922) *J. biol. Chem.* **52**, 2.
Werthemann, A. (1958) *Praxis*, **47**, 151.

Clinical Picture

Clinically all cases are strikingly similar. Usually the patient has been in reasonable health until a few days or at most a few weeks, before admission; and he is capable of giving a detailed history (unless obstruction has already taken place). During the next day or two, however, he becomes unable or unwilling to cough up his copious sputum, and—under the influence of hypoxia and CO_2 retention—more and more restless, confused, and apprehensive. This stage is followed by gradual withdrawal, and finally coma. (In some rapidly progressive cases the stage of excitement is short or absent.)

On physical examination in the pre-coma stages the patient presents the now well-known picture of CO_2 retention. He has warm extremities, a full bounding pulse, and a slightly raised blood-pressure (Westlake et al. 1955, Seiker and Hickam 1956). Breathing is rapid and shallow. In contrast to the more common chronic emphysematous respiratory failure, these patients look pallid, and later grey-blue, rather than cyanosed. The absence of classical cyanosis can deceive even the most experienced clinicians.

In the early phase of respiratory obstruction with asphyxia, the CO_2 retention, acidæmia, and hypoxia act on the respiratory centre to produce an exaggerated effort by the main and accessory muscles of respiration. Movements of the chest wall thus appear adequate; and only close inspection will reveal paradoxical indrawing of the intercostals on inspiration. Other signs point to the primary lung condition; but the breath-sounds are diminished in all regions, while coarse rales can be heard over the obstructing areas, usually the lower lobes.

The temperature is normal or below normal, either because reaction to infection is poor, or possibly as a direct result of CO_2 retention with increased loss of heat (Brown 1930). In the absence of fever, the widespread rales may be mistaken for signs of acute left ventricular insufficiency, and powerful sedatives may be prescribed.

At a later stage the blood-pressure falls and peripheral circulatory failure becomes obvious. By this time hypoxia and CO_2 retention are such as to depress rather than to stimulate respiration (Seevers 1944): towards the end respiration becomes uneven, irregular, and shallow, ceasing altogether some three or four minutes before cardiac standstill.

Illustrative Case-histories

During the eight months ending in March, 1958, 9 patients were admitted to the Queen Elizabeth Hospital, Birmingham, in whom this syndrome was present or developed and in whom tracheotomy was performed to relieve respiratory obstruction (table I). A typical history is that of the first patient, a working electrician of 73 with recurrent winter bronchitis.

Five days before admission he developed influenza and was treated symptomatically. Two days later his doctor diagnosed left-lower-lobe pneumonia: his temperature was then 103°F and he was coughing up copious purulent sputum. Next day he had little sputum and became confused; and during the night before admission he lapsed into coma.

On examination he was cyanosed, with a temperature of 97°F, shallow respirations of 30 per min., a pulse-rate of 96, and a blood-pressure of 100/70 mm. Hg. There was dullness over the left lower lobe; and, though breath-sounds were inaudible, sputum could be heard rattling in the trachea during occasional feeble attempts at coughing. Some fifteen minutes after oxygen therapy was started (with disposable mask at 5–6 litres per minute) his arterial O_2 saturation was only 78%.

Tracheotomy was performed and deep tracheal aspiration produced several ounces of sputum. No anæsthetic was

TABLE I—SUMMARY OF CLINICAL DETAILS

No.	Age and sex	Previous disease	Acute episode	Infecting organism	Duration of illness before tracheotomy (days)	Arterial oxygen saturation before tracheotomy (%)	Condition at tracheotomy	Post-operative "anoxic" mental changes	Duration of hospital treatment	Outcome
1	73 M	Chronic bronchitis	Lobar pneumonia	Pneumococcus	5	78*	Comatose	No	23 days	Back at work as electrician
2	51 M	Chronic bronchitis	Lung abscess	Pneumococcus *H. influenzæ*	37	..	Semi-comatose	Yes	87 days	Returned to work but later relapsed and died
3	63 M	Pneumonectomy 28 hours before tracheotomy	Acute bronchitis	Staphylococcus	1	71*	Comatose	No	34 days	Empyema and acute nephritis were late complications. Now (14 months later) dying from secondaries
4	83 F	Bronchitis	Bronchopneumonia	Staphylococcus	? 3†	64	Semi-comatose	Yes	31 days	Back to normal, living alone
5	63 F	Asthma	Bronchopneumonia	..	10	..	Comatose	..	3 hours	Died during tracheotomy
6	54 M	Pneumonectomy in 1954	Pulmonary infarction	..	8	59	Conscious	..	12 hours	Died 8 hours after tracheotomy
7	50 M	Chronic bronchitis, mitral stenosis, aortic incompetence, congestive failure	Acute bronchitis	..	7	..	Comatose	No	46 days	Back at work as a packer
8	61 F	Chronic bronchitis, epilepsy (3 fits on day of admission)	Bronchopneumonia	Pneumococcus	4	88	Conscious	No	59 days	Back at work as a housekeeper
9	56 M	Chronic bronchitis	Lobar pneumonia, auricular fibrillation	Pneumococcus	7	..	Comatose	..	5 days	Died 20 minutes after tracheotomy: cardiac arrest before respiratory failure from (?) ventricular fibrillation

* On oxygen therapy, 5 litres per minute. † Lived alone; found by a neighbour in semicoma, unable to give history then or later.

necessary. Respiration ceased at this point and artificial respiration was given by hand for fifteen minutes. Shortly after spontaneous respiration was re-established he regained consciousness. Further treatment was with tetracycline and digoxin. The tracheotomy tube was removed on the ninth day, by which time the patient was ambulant.

The third patient, a fit man of 63, in whom mass X-ray had shown a rounded shadow due to carcinoma, had a left pneumonectomy performed.

For the first twenty-four hours after this, his progress was satisfactory and then he became increasingly dyspnœic with a high fever and copious yellow sputum, from which *Staphylococcus aureus* was cultured. Twelve hours later he was exhausted, afebrile, and too ill to cough with a respiration-rate of 39 per min., a pulse-rate of 140, and a blood-pressure of 90/40. Bronchoscopy revealed bronchi full of creamy pus, which was carefully sucked out. One hour later, he was worse than ever, with an arterial oxygen saturation of 71% on adequate oxygen therapy.

After further bronchoscopy and the onset of paroxysmal tachycardia, tracheotomy was performed. The patient recovered.

Of 9 desperately ill patients 6 survived and 3 died; and I believe that all would have died without a tracheotomy. 1 patient died during the operation, and the other 2 died eight hours and twenty minutes after it.

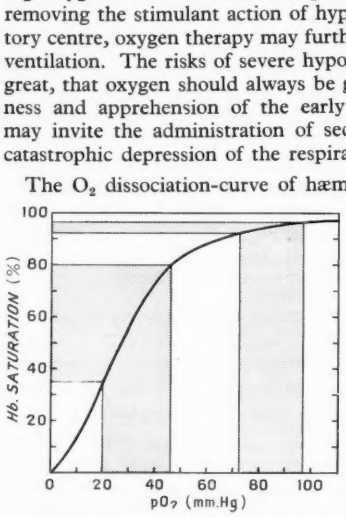
Physiological Changes

The management of these patients is greatly helped by an understanding of the physiological disturbance.

Partial respiratory obstruction first limits the ability to increase pulmonary ventilation normally. Later it begins to interfere even with resting alveolar gas-exchange; and, with the onset of alveolar underventilation, the body is unable to rid itself of normal amounts of CO_2. Despite some compensatory increase in plasma-bicarbonate, the arterial pH falls: and, because the rise in bicarbonate is slow compared to the accumulation of CO_2 the more acute the disturbance, the greater the acidæmia. Concurrently, failure of alveolar ventilation and a rising partial CO_2 pressure (pCO_2) leads to a falling partial O_2 pressure (pO_2) and a consequent fall in arterial O_2 saturation.

Because, owing to underventilation, lungs are unable to rid the body of CO_2, the correction of the hypoxia by giving oxygen will not relieve CO_2 retention: indeed, by removing the stimulant action of hypoxia on the respiratory centre, oxygen therapy may further diminish alveolar ventilation. The risks of severe hypoxia, however, are so great, that oxygen should always be given. The restlessness and apprehension of the early stages of asphyxia may invite the administration of sedatives with further catastrophic depression of the respiratory centre.

The O_2 dissociation-curve of hæmoglobin (see figure) shows that by the time acute respiratory obstruction results in clinically obvious cyanosis (80–85% arterial O_2 saturation) even slight depression of alveolar ventilation, either by further obstruction or by sedation, results in very severe hypoxia. Once the stage of hypoxia and CO_2 retention is reached, the process is self-perpetuating and



The figure shows that while a fall of alveolar or arterial oxygen tension of 25 mm. Hg at normal levels of arterial oxygen saturation (97%) causes a fall of only 4% in saturation, a similar 25 mm. Hg fall at 80% saturation causes a fall of 45% in saturation. Acidæmia displaces the curve downwards and to the right.

progressive. This is in contrast to chronic emphysematous respiratory failure, where the respiratory centre becomes gradually attuned to the rising pCO_2 and where moderate hypoxia, causing clinical cyanosis, is fairly well tolerated (Westlake et al. 1955, Seiker and Hickam 1956).

Discussion

In recent years tracheotomy has been used by thoracic surgeons as a prophylactic measure in poor-risk patients before operations such as œsophagectomy and pneumonectomy (Reynold 1950, Atkins 1951); and physicians in close contact with thoracic surgical centres have come to recognise that retention of sputum is not confined to surgical practice. However, despite reports by Pitman and Wilson (1955), Walker et al. (1958), Barrowcliff and Prior (1957), and Anderson and Niblock (1957), correspondence in the medical journals during the 1957 influenza epidemic showed that retention of sputum is not always recognised as the commonest cause of death in acute respiratory illness (Roberts 1957, Sheldon 1957).

TABLE II—ARTERIAL GAS-TENSION CHANGES WITH TRACHEOTOMY

Case	Before tracheotomy		One hour after tracheotomy	
	pO_2 (mm. Hg)	pCO_2 (mm. Hg)	pO_2 (mm. Hg)	pCO_2 mm. Hg)
4	37	90	39	79
7	31	110	34	99·5
8	70	54	67	50
x (post-operative)	55	71	53	62
Mean	48·3	81·3	48·3	72·6

pO_2 and pCO_2 were measured directly by the method of Riley et al. (1945). All measurements were made after the patient had been without oxygen for ten minutes.

Since airway maintenance is a mechanical problem, it calls for a mechanical solution; and tracheotomy has many advantages.

1. It allows repeated aspirations, even by personnel unskilled in endoscopy.

2. It enables oxygen to be given by endotracheal catheter without the distress caused in uncooperative patients by tents, masks, or nasal catheter.

3. It reduces dead space by approximately half; and this often makes all the difference between a rising and a falling pCO_2. Use of the largest possible tube reduces airway resistance to a minimum.

The effects of tracheotomy on blood-gas tension in 3 cases of the present series and in 1 postoperative case are shown in table II. Table III gives details of the progress of case 4 as measured by blood-gas changes. The failure of arterial pO_2 to be influenced by tracheotomy (tables II and III) remains unexplained: it is most likely to be related to disturbances of the ventilation/perfusion ratios.

If tracheotomy is done in good time, it is one of the safest operations in surgery, and there have been no major complications of it in any department of the hospital in the past two years. Provided someone skilled in bronchoscopy can be obtained in a few minutes, there is advantage in performing bronchoscopy first; for it allows visual proof of the clearing of the bronchial tree, and it ensures an adequate airway. But if no such person is at hand, tracheotomy should be undertaken forthwith. General anæsthesia is contraindicated: even sedatives are dangerous. The onset of asphyxia followed administration of chloral hydrate gr. 15 in case 5 and morphine sulphate gr. $^1/_6$ in case 7.

Tracheotomy deprives the patient of the ability to cough effectively; and, since clearing the respiratory tract of sputum is the prime condition of recovery, aspiration has to be very frequent at first.

At the initial clearance a soft rubber catheter which is lubricated with water and which has at least a terminal hole and one at the side, is introduced repeatedly over some twenty minutes until no further sputum is obtained. Each introduction stimulates coughing, and each bout of coughing brings fresh sputum within the range of the catheter. During the first few hours aspiration is performed every ten minutes by the clock and thereafter as often as necessary.

Oxygen is administered saturated with water vapour at body temperature, at the rate of 2–3 litres per minute, by endotracheal catheter (Barach 1948). At this rate it maintains oxygenation without inducing much further carbon-dioxide retention. If oxygen is not available gentle continuous suction of air through a cathether, introduced as far down as the carina, will reduce dead space.

The drying effect of oxygen and suction on the respiratory tract can result in considerable loss of fluid, unless a steam tent is used or the oxygen is saturated with water vapour at body temperature. This must be taken into account when calculating fluid balance. Drying of the secretions, moreover, may lead to crusting and secondary obstruction, unless the tracheotomy tube is changed regularly every second or third day.

Several reports of cases of CO_2 retention treated by intermittent-positive-pressure respiration through a cuffed tracheotomy tube have been published (Boutourline-Young and Whittenberger 1951, Stone et al. 1953, Lovejoy et al. 1954, Seiker and Hickam 1956, Hugh-Jones 1958); but apparently moribund patients can recover consciousness rapidly with tracheotomy and suction alone. (Positive-pressure respiration may be indicated in more chronic conditions.) Some evidence suggests that a sudden reduction in the pCO_2 leads to ventricular arrhythmias or a sudden fall in blood-pressure (Miller et al.

TABLE III—ARTERIAL GAS-TENSION LEVELS IN CASE 4

—	—	Before tracheotomy	After tracheotomy							
			1 hour	24 hours	48 hours	5 days	9 days	12 days		31 days
								O	C	H
At rest, without oxygen	pO_2 (mm. Hg)	37	39	36	40	36	44	53	41	53
	pCO_2 (mm, Hg)	90	79	72	73	66	65	50	69	64
	pH	7·239	7·280	..	7·343	7·389	7·369	7·410	7·341	7·375
After 10 minutes on oxygen at 5 litres per minute	pO_2 (mm. Hg)	..	64	..	129*	104*	118*	..	..	..
	pCO_2 (mm. Hg)	..	89	..	85	78	70	..	..	..

O, tracheotomy open. C, tracheotomy tube removed and wound sealed off. H, tracheotomy wound healed. * Uncorrected.

1952, Brown 1955); and this may have been the mode of death in case 9. This was the only patient in the series in whom artificial respiration was given with an anæsthetic bag and a Waters CO_2-absorber while the tracheotomy was performed.

Of the other 2 fatal cases, it seems likely that in case 6 the amount of pulmonary tissue had been reduced by pneumonectomy and pulmonary infarction beyond the point at which life could be sustained; and that in case 5 the operation was delayed too long. At necropsy in case 5 the trachea and bronchi were full of thick sputum, up to the level of the vocal cords.

The postoperative progress of some of these patients—particularly of the old lady of 83, who was quite deranged mentally for almost two weeks—confirms the reports of Bedford (1955, 1956) and of Courville (1936) on the effects of severe or prolonged anoxia on the brain. Although these patients showed no evidence of permanent brain damage or character change, I now would say that the operation was undertaken too late in all but case 8.

I have had regrets only when a tracheotomy has not been done—never when it has been done.

Summary

In a group of 9 patients with primary respiratory disease retention of sputum led to asphyxia. 6 were successfully treated by tracheotomy and clearance of the bronchi by suction.

The advantages of tracheotomy and its management in this type of patient are discussed.

I should like to thank Dr. A. Brian Taylor, Dr. A. G. W. Whitfield, and Dr. Kenneth Donald for encouragement in treating patients under their care, and my surgical colleagues for their speed and efficiency in performing the tracheotomies. The apparatus on which the blood-gas studies were performed was purchased out of a grant by the United Birmingham Hospitals' endowment fund.

REFERENCES

Anderson, J. L., Niblock, W. McN. (1957) *Lancet*, ii, 1337.
Atkins, J. P. (1951) *J. Amer. med. Ass.* **146,** 241.
Barach, A. L. (1948) Physiologic Therapy in Respiratory Disease. Philadelphia.
Barrowcliff, D. F., Prior, A. P. (1957) *Lancet*, ii, 1230.
Bedford, P. D. (1955) *ibid.* ii, 259.
— (1956) *Proc. R. Soc. Med.* **49,** 609.
Blair, J. N. (1955) *Canad. med. Ass. J.* **72,** 766.
Boutourline-Young, H. J., Whittenberger, J. L. (1951) *J. clin. Invest.* **30,** 838.
Brown, E. B. (1955) *Proc. Soc. exp. Biol., N.Y.* **90,** 319.
Brown, E. W. (1930) *Naval med. Bull. Wash.* **28,** 523.
Courville, C. B. (1936) *Medicine, Baltimore*, **15,** 129.
Echols, D. H., Llewellyn, R., Kirgis, H. D., Rehfeldt, F. C., Garcia-Bengochea, F. (1950) *Surgery*, **28,** 801.
Haight, C., Ranson, H. K. (1941) *Ann. Surg.* **114,** 243.
Hugh-Jones, P. (1958) *Proc. R. Soc. Med.* **51,** 104.
Lassen, H. C. A. (1953) *Lancet*, i, 37.
Lewy, R. B., Sibbitt, J. W. (1951) *Amer. Practit.* **2,** 527.
Lovejoy, F. W., Yu, P. N. G., Nye, R. E., Joos, H. A., Simpson, J. H. (1954) *Amer. J. Med.* **16,** 4.
Maciver, I. N., Frew, I. J. C., Matheson, J. G. (1958) *Lancet*, i, 390.
Miller, F. A., Brown, E. B., Buckley, J., van Bergen, F. H., Varco, R. L. (1952) *Surgery*, 32, 171.
Pitman, R. G., Wilson, F. (1955) *Lancet*, ii, 523.
Priest, R. E. (1952) *Ann. Otol., &., St. Louis*, **61,** 1039.
Reynold, J. T. (1950) *Arch. Surg.* **60,** 211.
Riley, R. L., Preommel, D. D., Franke, R. E. (1945) *J. biol. Chem.* **161,** 621.
Roberts, G. B. S. (1957) *Lancet*, ii, 944.
Sandiford, H. B. C. (1957) *ibid.* p. 823.
Seevers, M. H. (1944) *N.Y. St. J. Med.* **44,** 597.
Seiker, H. O., Hickam, J. B. (1956) *Medicine*, **35,** 389.
Sheldon, D. H. S. (1957) *Lancet*, ii, 1066.
Stone, D. J., Schwartz, A., Newman, W. V., Feltman, J. A., Lovelock, F. J. (1953) *Amer. J. Med.* **14,** 14.
Walford, A. S., Smith, A. C., Spalding, J. M., Cameron, D., Wilson, A. B. (1955) *Proc. R Soc. Med.* **48,** 947.
Walker, W. C., Douglas, A. C., Leckie, W. J. H., Pine, S. A., Grant, I. W. B. (1958) *Lancet*, i, 449.
Westlake, E. K., Simpson, T., Kaye, M. (1955) *Quart. J. Med.* **24,** 155.
Williams, M. H. (1951) *Amer. J. Surg.* **90,** 641.

TRACHEOBRONCHIAL TOILET THROUGH A TRACHEOSTOME

LIONEL H. OPIE
M.B. Cape Town, M.R.C.P.
RHODES SCHOLAR, DEPARTMENT OF NEUROLOGY AND LINCOLN COLLEGE

A. CRAMPTON SMITH
M.B. Edin., F.F.A. R.C.S.
OF THE NUFFIELD DEPARTMENT OF ANÆSTHETICS

From the Respiration Unit, United Oxford Hospitals

TRACHEOTOMY is now often performed for conditions which impair the patient's ability to cough—e.g., in paralysing disorders such as poliomyelitis (Lassen 1953), and the unconscious state, especially due to head injury (Bryce-Smith 1950). In these patients it is necessary to aspirate the tracheobronchial tree with a catheter; and for such toilet to be fully effective, secretions should be removed from both sides of the chest. In this investigation we examined some of the techniques that have been employed for this purpose, and assessed their value.

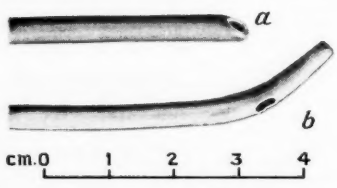


Fig. 1—(a) Soft rubber whistle-tipped catheter, as used in fig. 2. (b) Angulated bronchoscopy catheter, as used in figs. 3 and 4 with holes at angle and at tip.

We studied fifteen patients who were having intermittent positive, pressure respiration from Radcliffe respiration pumps (Russell et al. 1956) through a right-angled tracheotomy tube (Spalding and Smith 1956).

Rubber catheters (French gauge 12 or 15, English gauge 6 or 8) were filled with radio-opaque dye (' Dionosil Oily '). The external end of the catheter was clipped to prevent the dye from escaping into the lungs. Immediately before a routine (portable) chest radiograph was taken, the respiration pump was temporarily disconnected from the supine patient, and when the catheter had been introduced through the tracheostome as far as possible the X-ray plate was exposed. With this technique a soft rubber " whistle-tipped " catheter (fig. 1a) went into the right lower zone 9 out of 10 times. A typical result is shown in fig. 2.

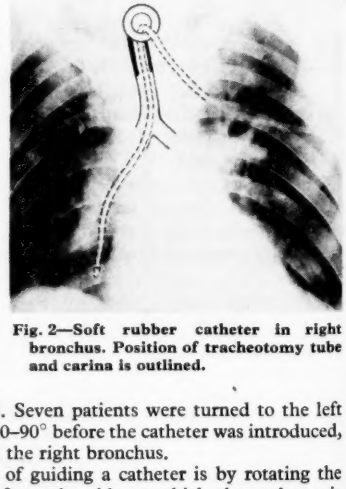


Fig. 2—Soft rubber catheter in right bronchus. Position of tracheotomy tube and carina is outlined.

It is sometimes assumed that a catheter can be guided into one side by first turning the patient on to the appropriate side to assist the catheter's entry by gravity (Maciver et al. 1958). Seven patients were turned to the left through an angle of 60–90° before the catheter was introduced, but it always entered the right bronchus.

Another technique of guiding a catheter is by rotating the patient's head away from the side at which the catheter is aimed (Macrae et al. 1954). After turning the head to the right before insertion the catheter reached the right side 6 out of 7 times.

In all, the soft rubber catheter was passed through the

tracheotomy tube 24 times; but only twice could its presence in the left main bronchus be demonstrated.

Catheters with angulated tips were used also. A hard Tiemann catheter or a soft "bronchoscopy" catheter* (fig. 1b) was guided through the tracheostome so that the tip of the catheter pointed to the left as it emerged from the tracheotomy tube into the trachea.

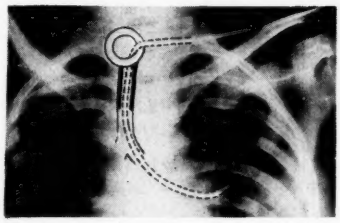


Fig. 3—Bronchoscopy catheter in left bronchus.

The Tiemann catheter entered the left side in 1 of 4 attempts; but we stopped using it because of the risk of damaging the bronchial tree (Harries and Lawes 1955).

The softer bronchoscopy catheter justified expectations and reached the left side 6 out of 7 times (fig. 3). But there were 2 other failures because the tracheotomy tube extended towards the right main bronchus almost to the carina (fig. 4). When the tube was shortened, the bronchoscopy catheter could be guided into the left bronchus.

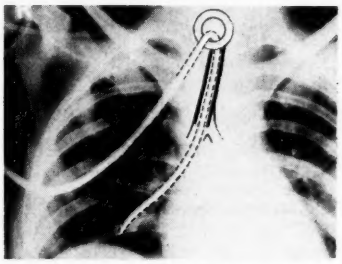


Fig. 4—Bronchoscopy catheter unable to enter left bronchus: tracheotomy tube extends almost to carina in direction of right bronchus.

Summary

When passed through a tracheotomy tube, a soft rubber catheter entered the right bronchus in over 90% of attempts, whether the patient was supine, lying on the left side, or had the head rotated to the right.

An angulated "bronchoscopy" catheter was guided into the left bronchus with a reasonable prospect of success.

We wish to thank Dr. Ritchie Russell and Dr. J. M. K. Spalding for advice and helpful criticism, and the staff of the X-ray department, Churchill Hospital, for their assistance. Sister J. Mair and the staff of the respiration unit made this investigation possible by their willing cooperation.

REFERENCES

Bryce-Smith, R. (1950) *Brit. med. J.* ii, 322.
Harries, J. R., Lawes, W. E. (1955) *ibid.* i, 722.
Lassen, H. C. A. (1953) *Lancet*, i, 37.
Maciver, I. N., Lassman, L. P., Thomson, C. W., McLeod, I. (1958) *ibid.* ii, 544.
Macrae, J., McKendrick, G. D. W., Sefton, E. M., Walley, R. V. (1954) *ibid.* ii, 21.
Russell, W. R., Schuster, E., Smith, A. C., Spalding, J. M. K. (1956) *ibid.* i, 539.
Spalding, J. M. K., Smith, A. C. (1956) *ibid.* ii, 1247.

*Bronchoscopy catheters are made by the G.U. Manufacturing Company, Devonshire Street, London, W.1.

"... I have yet to attend an international conference which did not illustrate repeatedly how firmly men and women believe, perhaps correctly, that professional advancement is closely knit with long-winded and excessive publication, particularly in the highly specialized fields of learning.... Travel to Babel is swift and no expense is spared; and if there are seventy coaches for the scientists there are certainly thirty for the arts."—Dr. C. F. A. PANTIN, *Camb. Univ. Rep.* March 4, 1959, p. 898.

THROMBOENDARTERECTOMY FOR ATHEROSCLEROTIC BLOCKAGE OF FEMORAL AND POPLITEAL ARTERIES

H. S. SHUCKSMITH
T.D., M.B., B.Sc. Leeds, F.R.C.S.
SURGEON, GENERAL INFIRMARY AND ST. JAMES' HOSPITAL, LEEDS

G. WILSON
M.B. Leeds, F.R.C.S.
SENIOR SURGICAL REGISTRAR, UNITED LEEDS HOSPITALS

THROMBOENDARTERECTOMY through longitudinal incisions in the lower aorta and common iliac arteries was introduced by Dos Santos (1947), and this method of removing atheromatous plaques and thrombus from these large vessels is well established (Wylie 1952). Thromboendarterectomy of the femoral and popliteal arteries was described by Reboul and Laubry (1950) and Forty (1953), but has since been made easier by the perfection of loop strippers (Cannon and Barker 1955): the stripping loops are introduced through short arteriotomy incisions and most of the procedure is performed "blind". For atherosclerotic blockage of the femoral and popliteal arteries the results recorded by Cannon and Barker (1955), Warren (1957), and Cannon et al. (1958) compare favourably with those of the bypass graft. Stripping has the advantage that no foreign body remains in the wound.

We are trying this method for patients with rest pain, early gangrene, or incapacitating claudication, when the lower popliteal artery is patent and there is little or no calcification in the femoro-popliteal artery.

Operative Technique

The patient lies supine, and the popliteal artery is exposed through a longitudinal incision on the medial side of the knee, retracting sartorius backwards and dividing adductor magnus or the medial head of gastrocnemius as required for access to the proximal or distal part of the vessel. The common femoral artery and its divisions are exposed, also through a longitudinal incision. Patency of the popliteal artery is verified by palpation and incision; 40 mg. of heparin is given intravenously, and clamps are applied to the common femoral artery and its divisions and to the distal popliteal artery.

When the block is extensive and the common femoral artery contains atheromatous deposits, a 1–1·5 cm. incision is made in the popliteal artery, centred over the distal edge of an atheromatous deposit. Dissection of the central atheromatous core in a surrounding plane of cleavage is performed, and the core is freed upwards sufficiently to be threaded into a loop stripper of suitable size. The stripper is then pushed gently upwards and rotated as necessary until it sticks. A 1–1·5 cm. incision is made in the common femoral artery; the atheroma with thickened intima is freed in a plane of cleavage and a second loop stripper of suitable size is threaded over it and manipulated down the superficial femoral artery. If the two loops cannot be pushed together, the artery over the lower stripper is exposed, usually at the level of the adductor opening, and the stripper is guided along the artery with lateral pressure outside the artery wall, or if necessary a further arteriotomy incision is made. After the stripping loops have passed freely along the artery in the plane of cleavage, the central atheromatous core with thrombus is removed and the lumen washed out with heparin (10 mg. per 100 ml.) saline solution. The arteriotomy incisions are sutured, and when hæmostasis is satisfactory the wounds are closed around a small rubber drain. The distal edge of the intima in the popliteal artery must not be left loose; and after it has been trimmed as smooth as possible, any free edge may have to be tacked directly back to the vessel so as to prevent dissection by blood between the intima and media. Similarly, the intima around the origin of the profunda artery may have to be reattached to the common femoral artery.

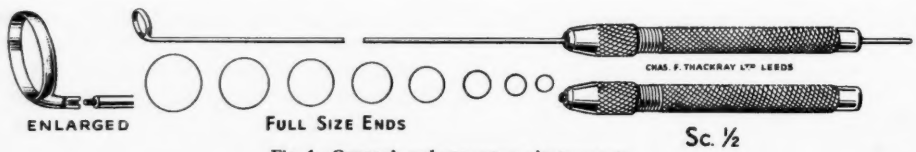
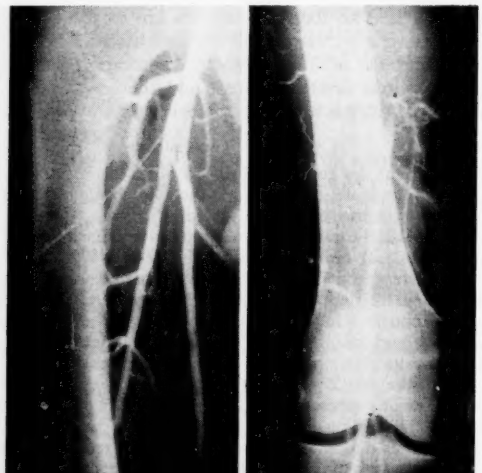


Fig. 1—Cannon's endarterectomy instruments.

When the block is confined to the proximal part of the popliteal artery, thromboendarterectomy can be carried out with one loop stripper introduced through the incision in the popliteal artery without exposing the common or superficial femoral arteries. The loop stripper enters the lumen again when it reaches the end of the atheromatous area in the lower part of the superficial femoral artery, and so allows the atheromatous core to be withdrawn.

When there are no gross atheromatous deposits in the common femoral artery and a second stripper has to be used from the upper end, it is introduced through an incision in the proximal part of the superficial femoral artery.

Heparin 50 mg. is given 4-hourly for 24 hours after operation. Phenindione is started on the 4th postoperative day and continued for weeks or months keeping the prothrombin-time at about twice the normal level (Robb 1956, Martin and Gaylis 1957).



(a) (b)

Fig. 2—The femoral (a) and popliteal (b) arteriograms in case 1 showing atherosclerotic block in the distal part of the right superficial femoral artery.

Fig. 2c—The central atheromatous core stripped from the right common and superficial femoral and popliteal arteries in case 1.

Note.—The loop strippers ought to be so constructed that they may be gently rotated during the stripping process, and the instruments made for us by Messrs. C. F. Thackray (fig. 1) in one piece of metal are satisfactory because there is no danger of the loop becoming detached from the handle.

Illustrative Case-reports

Case 1.—A labourer, aged 58, had intermittent claudication in the right calf after walking 250 yards, and pain in the foot which prevented sleep. The blood-pressure was normal, the popliteal and ankle pulses were absent, and the arteriogram (fig. 2, a and b) showed a block in the distal part of the superficial femoral artery. At operation, an atheromatous core 30 cm. long was removed in one piece with immediate restoration of the ankle pulses (fig. 2, c). Despite phenindione control from the 4th postoperative day, he developed a deep-vein thrombosis in the calf; but this resolved after treatment with external support. 9 months after operation the ankle pulses are good and he is back at work.

(a) (b)

Fig. 3—The popliteal arteriogram (a) and the thromboendarterectomy specimen (b) in case 2.

Case 2.—A gamekeeper, aged 46, had intermittent claudication in the right calf after walking 200 yards. The blood-pressure was normal, the popliteal and ankle pulses were absent. An arteriogram showed a block about 2 in. long in the proximal part of the popliteal artery (fig. 3, a). When the popliteal artery was exposed, pulsation was felt just below the adductor opening and the block in the artery (fig. 3, b) was removed through an arteriotomy incision 1 cm. long in the popliteal artery, the loop stripper re-entering the lumen when it reached the lower part of the superficial femoral artery. Ankle pulses were restored, and there is full function 8 months later.

Case 3.—A paper-worker, aged 41, had intermittent claudication of the right calf after walking 300 yards, and the foot was cold. Popliteal and ankle pulses were absent, the blood-pressure was normal. A femoral arteriogram showed a block in the superficial femoral artery (fig. 4, a). Thromboendarterectomy was started in the popliteal artery, but the stripper stuck at the level of the adductor opening. The common femoral artery was then opened and endarterectomy was started from above; but, after pushing the stripper down the superficial femoral artery for a few centimetres, it re-entered

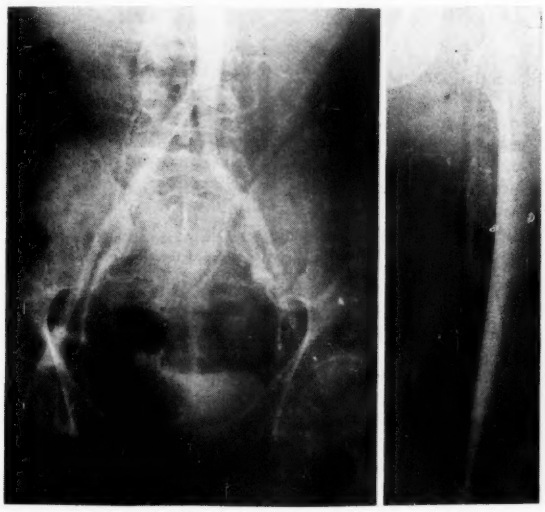
(a) (b)

Fig. 4—Arteriogram (a) showing block in lower part of superficial femoral artery in case 3, and (b) the atheromatous core removed.

the lumen of the superficial femoral artery. Using the two strippers together, we were then able to overcome the obstruction to the lower stripper at the level of the adductor opening and remove the atheromatous core 8 cm. long (fig. 4, b). The ankle pulses were restored.

Case 8.—A labourer, aged 59, had rest pain in the left foot with early gangrene of the toes, œdema of the dorsum of the foot, and a painful ulcer on the heel. The pulse at the left common femoral point was weak and no other pulses could be felt in the limb. The blood-pressure was 150/90 mm. Hg. The aortogram (fig. 5, a and b) showed a patent profunda femoris artery but a complete block of the superficial femoral artery. At operation the common femoral artery was exposed and found to be completely blocked. After dissection of the atheromatous core, a loop stripper was passed over the core up the external iliac artery and a 10 cm. core withdrawn. This procedure established good bleeding and the common femoral artery was then clamped. Thromboendarterectomy of the superficial and popliteal arteries was then performed, a further 35 mm. core being removed (fig. 5, c). Ankle pulses were not restored but the foot became warm, the œdema subsided and the ulcer healed.

6 weeks later the patient again had severe pain in the foot, preventing sleep. The foot was still warm and an aortogram showed wide patency of the external iliac artery (fig. 6, a), and patency of the common and superficial femoral arteries (fig. 6, b); but there was a block in the popliteal artery (fig. 6, c). Above-knee amputation had to be carried out because



(a) (b)

Fig. 5—(Case 8). The arteriogram (a) shows a patent external iliac and common femoral arteries with filling of the profunda femoris artery on the left side. The left superficial femoral artery is completely blocked (b).

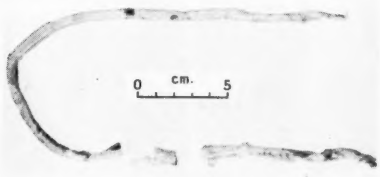
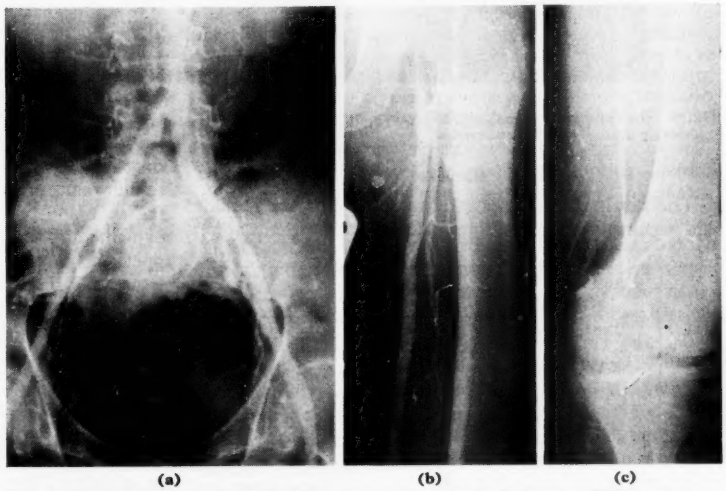


Fig. 5c—The atheromatous core from the external iliac, common femoral, superficial femoral, and popliteal arteries (case 8).

of the severe pain, although the foot remained warm. During the amputation the superficial femoral artery was seen to pulsate well and was widely patent. Examination of the amputated leg showed that the cause of the failure was a small ulcerated patch of atheroma distal to the popliteal arteriotomy: proximal to it was a red thrombus undergoing early organisation. Histology of part of the superficial femoral artery showed that



(a) (b) (c)

Fig. 6—Six weeks after thromboendarterectomy (case 8), the left external iliac, common femoral (a), and superficial femoral arteries (b) are patent, but the popliteal artery (c) has thrombosed.

it was lined with fibrin, which was cover with flattened endothelial cells (fig. 7).

Fig. 7—A section of the superficial femoral artery taken from the amputated limb (case 8). The vessel is widely patent, and the media is covered by a layer of fibrin on the surface of which is a layer of flattened endothelial-like cells. Werhoeff's elastic stain (×6).

Case 9.—An engineer, aged 58, with Felty's syndrome, had previously had an above-knee amputation for gangrene of the left foot; and now, 18 months later, he had gangrene of the right big toe. An arteriogram (fig. 8, a and b) showed no complete block but gross atherosclerosis of the superficial femoral and popliteal arteries. Thromboendarterectomy was attempted, but proved impossible because the knives were quickly held up by calcification. A bypass graft was impracticable because of severe atherosclerosis of the distal part of the popliteal vessel. Above-knee amputation was performed.

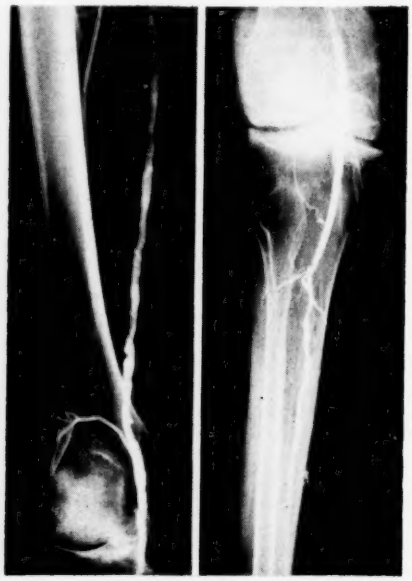


Fig. 8—The femoral (a) and popliteal (b) arteriogram in case 9, showing extensive atherosclerosis.

Results

The results of thromboendarterectomy of the femoral and popliteal arteries performed in thirteen patients were:

Case	Reason for operation	Restoration of ankle pulses	End-result
1	Claudication	Yes	Good
2	"	"	"
3	"	"	"
4	"	"	"
5	"	"	"
6	"	"	"
7	"	"	"
8	Gangrene	No	Amputation
9	"	—	"
10	"	Yes	Died after hæmatemesis
11	"	"	Amputation: secondary hæmorrhage
12	"	No	Amputation
13	"	Yes	Good

In ten cases the operation restored one or more ankle pulses, but one of these patients (case 10) died on the 21st postoperative day from hæmatemesis arising from a chronic gastric ulcer, and another (case 11) had a secondary hæmorrhage from the common femoral artery caused by staphylococcal infection of a hæmatoma which had to be evacuated on the 5th postoperative day. This patient had been given heparin for the first 4 days after operation. In the remaining eight patients in whom ankle pulses were restored, the results are satisfactory after periods of 5–9 months. Two patients who had gangrene (cases 9 and 12) were unsuitable for any form of reconstructive surgery and above-knee amputation was performed. In case 8 this was done at the end of an attempt at thromboendarterectomy, but in case 12, 3 weeks later. In case 9 gangrenous toes improved considerably until further popliteal thrombosis occurred in the 6th post-operative week and amputation had to be carried out for rest pain.

The best results have been obtained in intermittent claudication, and in two patients with gangrene of the toes it was possible to preserve the limb.

Discussion

Thromboendarterectomy is possible because a plane of cleavage can be found between an atheromatous plaque, with its adjoining thickened intima, and the diseased inner portion of the media (Julian et al. 1952). The intima is usually thickened between areas of atheroma, and this permits the loop stripper to be pushed along deep to it. If an area of relatively normal intima is reached, the stripper may re-enter the lumen of the artery. The media and adventitia remain after stripping and acquire a new endothelial lining within a few weeks (Reboul and Laubry 1950, Barker et al. 1955). This is well illustrated in our case 8 (fig. 7). The risk of aneurysm formation (Wylie et al. 1951) is small: Barker et al. (1955) recorded only one aneurysm developing after over a hundred thromboendarterectomies. This risk may be greater if endarterectomy is attempted in the presence of extensive calcification of an atheromatous plaque, for a deeper bite may be taken from the artery wall. Thrombo-endarterectomy has the advantage of conserving grafts: these are expensive, and homografts may be difficult to obtain. Whereas in our experience of synthetic bypass grafts there is considerable oozing for several minutes after release of the clamps, thromboendarterectomy can be done with very little loss of blood. Other advantages are that no foreign body is introduced permanently into the tissues, and there is no risk of the thrombosis that may result from altered turbulence at the site of an end-to-side anastomosis. The absence of any considerable fall in blood-pressure on release of the clamps may be explained by the small blood-loss and by the fact that the operation takes less time than grafting and this produces less anoxic dilatation of the limb vessels.

In view of the small but definite risk of rupture of the arterial wall during thromboendarterectomy with the loop strippers, we think it unwise to attempt stripping unless a bypass graft is available for use if the artery is damaged beyond repair.

Ultimate success depends upon the patency of the distal arteries. Barker (1955) recommends arteriography at operation, but this carries a further risk of thrombosis, and we prefer to rely on the degree of back bleeding when the arteriotomy wound is made in the popliteal artery,

and the knowledge that one of the tibial arteries or the peroneal artery is likely to be patent (Dible 1956).

Administration of heparin for 4 days after operation is recommended by Cannon and Barker (1955), but in one of our patients (case 11), the use of heparin for 4 days was followed by a large hæmatoma, leading to infection, secondary hæmorrhage, and amputation. Hence we now give heparin for only 24 hours. In accordance with the practice of Robb (1956) and Martin and Gaylis (1957), long-term anticoagulants are given on the 4th post-operative day and continued for an indefinite period. By the use of phenindione, the prothrombin-time is kept about twice the normal value, but in spite of this deep and superficial venous thromboses develop and the value of the drug is not yet established.

Summary

Atherosclerotic blocks of the femoral and popliteal arteries in 13 patients have been treated by thrombo-endarterectomy with a loop stripper.

The better results have been in the relief of intermittent claudication, but limbs have been salvaged even when toes were gangrenous.

The method has some advantages over bypass grafts.

We are indebted to Dr. Jack A. Cannon for discussing his method with one of us; to Dr. P. G. Keats and Dr. M. G. Sumerling for the arteriograms; to Dr. T. W. Sutherland for the histology; to Mr. A. L. Pegg for the photographs, and to Messrs. C. F. Thackray for fig. 1.

REFERENCES

Barker, W. F. (1954) *Surgery*, **36**, 233.
— Cannon, J. A., Zeldis, L. J., Ah'tye, P. (1955) *Surg. Forum*, **6**, 266.
Cannon, J. A., Barker, W. F. (1955) *Surgery*, **38**, 48.
— — Kawakami, I. G. (1958) *ibid.* **43**, 76.
Dible, J. H. (1956) *in* Peripheral Vascular Disorders (edited by P. Martin); p. 340. Edinburgh.
Dos Santos, J. C. (1947) *Mém. Acad. Chir.* **73**, 409.
Forty, F. (1953) *Proc. R. Soc. Med.* **46**, 125.
Julian, O. C., Dye, W. S., Olwin, J. H., Jordan, P. H. (1952) *Ann. Surg.* **136**, 459.
Martin, P., Gaylis, H. (1957) *Brit. med. J.* ii, 371.
Reboul, H., Laubry, P. (1950) *Proc. R. Soc. Med.* **43**, 547.
Robb, C. (1956) *Brit. med. J.* ii, 1027.
Warren, R. (1957) *Surg. Gynec. Obstet.* **104**, 571.
Wylie, E. J. (1952) *Surgery*, **32**, 275.
— Kerr E., Davies, O. (1951) *Surg. Gynec. Obstet.* **93**, 257.

INFANTILE SPASMS AND HYPSARRHYTHMIA

B. D. Bower
M.D. Birm., M.R.C.P., D.C.H.
LECTURER IN PÆDIATRICS, UNIVERSITY OF BIRMINGHAM

P. M. Jeavons
M.A., M.B. Cantab., D.P.M.
CONSULTANT PSYCHIATRIST, ALL SAINTS' HOSPITAL, BIRMINGHAM

From the Children's and All Saints' Hospitals and the University Department of Pædiatrics and Child Health, Birmingham

In 1841 W. J. West gave a graphic description of salaam spasms, a variety of infantile spasms, in a letter to *The Lancet*. The patient was his own child, and the letter was an appeal for help. Though others were aware of the condition at that time, no treatment had prevented the child's epileptic and intellectual deterioration.

Although there has recently been a revival of interest in infantile spasms, mainly on the Continent and in the United States, our understanding of this variety of epilepsy is hardly greater today than it was a hundred years ago, and our treatment is scarcely more successful than was the lancing of the gums and opiate administration practised on West's child. Publications outside Britain include those of Asal and Moro (1924), Zellweger (1948), Vasquez and Turner (1951), Gibbs and Gibbs (1952), Hess and Neuhaus (1952), Gastaut and Roger (1953), Gibbs et al. (1954), Thiébaut et al. (1955), Baird and Borofsky (1957), Chao et al. (1957), and Livingston et al. (1958). In this country only Illingworth (1955) and Pond (1958) have given adequate descriptions of the syndrome, and it is mentioned briefly or not at all in British pædiatric textbooks.

Many names have been used to describe the fits and their variants: *Blitzkrampfen*, *Nickkrampfen*, and *Salaam-krampfen* (Asal and Moro 1924), flexion spasms (Gastaut and Roger 1953), lightning spasms, massive spasms, salaam spasms, greeting spasms, jack-knife convulsions, nodding spasms, secousses, and infantile spasms. Although most of these are vivid, they are not comprehensive, and we have chosen the less colourful "infantile spasms" as a convenient term to cover all varieties of this type of epilepsy.

A grossly abnormal and characteristic electroencephalographic (E.E.G.) pattern is commonly found in patients with infantile spasms and is now usually known as hypsarrhythmia (Gibbs and Gibbs 1952). While the typical appearance, described by these workers, poses no problem, we have had difficulty in classifying less typical appearances; and, from E.E.G. tracings illustrated in some of the above publications, others seem to have had similar difficulty. We have therefore analysed the E.E.G.s of our patients using a scoring system designed to separate the characteristics of hypsarrhythmia from those of non-hypsarrhythmia epilepsy. By this means we have tried to establish the degree of correlation between hypsarrhythmia and infantile spasms.

Clinical Features

In the 3-year period from January, 1955, to December, 1957, twenty-two children attended the Children's Hospital suffering from infantile spasms. The clinical features of these patients form the basis of the following description:

The spasm.—This is a sudden, brief, generalised myoclonic jerk. The arms are flung outwards and forwards (as in the Moro reflex) or upwards, and the legs may flex or extend. The trunk or neck, or both, may flex—the nod, salaam, or jack-knife convulsion—or extend. A forward jerk of the shoulders may accompany neck flexion, or may even be the only movement. In the extensor type the eyes are often turned upwards. Sometimes there is a lateralising feature, such as turning of the head to one side, or greater jerking of an arm on one side. In both types, the flexor and extensor, there is usually a repetition of the spasm within a few seconds, after a cry which seems to be posticta1 rather than ictal, and is probably due to pain or fright. Alternations of spasm and cry (the number of which may vary considerably) often form a series.

There were fifteen patients with flexor spasms and seven with extensor spasms as the presenting feature (table I). Occasionally the alternative type of spasm occurred later in the same patient.

The mother of a baby with flexion spasms commonly complains that he has abdominal pain (case 6 below), and it is easy to understand why she makes this misinterpretation. The parents of three babies have noticed excessive production of tears before the spasm.

Apart from colic, other diagnoses which may require consideration when the spasm is flexor are the normal Moro reflex and masturbation. The position of the arms in the Moro reflex is similar to that of the spasm, but it is a "startle" response obtained after various stimuli, and is not repeated as a series. The movement of masturbation is rhythmic, slower, and accompanied by facial flushing and grunting.

Some workers do not mention the extensor type of spasm (Vasquez and Turner 1951, Hess and Neuhaus 1952, Gastaut and Roger 1953); others think it is a variety of infantile spasm (Chao et al. 1957). Thiébaut et al. (1955) mention turning up of the eyes. Possibly some workers regard extensor spasms as tonic spasms (decerebrate attacks), and Hess and Neuhaus (1952) discuss the difficulty in distinguishing the two groups clinically. We have taken the speed of attack as the criterion as to whether the case should be included—i.e., if the movement was rapid (" lightning ") it was regarded as an infantile spasm of extensor type—but the differentiation is not always easy.

We have avoided the term " minor motor seizure " as this has been used to describe several different types of attack. Bridge (1949) includes under this title attacks which would nowadays be termed temporal-lobe fits. On the other hand, some of Illingworth's (1955) patients, described as having minor motor seizures, had attacks similar to infantile spasms of extensor type. Nor have we used the term " akinetic attack " for there is no agreement on its meaning.

As a descriptive term it is used to mean a sudden dropping to the floor. From the name one would presume that it is an inhibitory attack, with loss of muscle tone. Bridge (1949), who evidently thinks this explanation is correct, includes salaam attacks under this heading. Livingston et al. (1958) regard akinetic attacks as similar to massive myoclonic attacks and nodding spasms, including them all under the heading of minor motor epilepsy. Gastaut (1954) classifies akinetic epilepsy as a variant of myoclonic epilepsy, not due to loss of tone.

For two reasons we doubt whether the patients in the under-3-year age-group have akinetic (i.e., inhibitory) attacks. Firstly, we have not found in our patients the E.E.G. patterns typical of the petit-mal triad, to which (according to Lennox 1945) akinetic epilepsy belongs. Secondly, infants who have salaam attacks when supine show flexion of the neck and trunk in the same way as children who are upright, which suggests that the attack is a massive myoclonic jerk.

TABLE II—AGE OF ONSET OF INFANTILE SPASMS

Age (mos.) ..	0–1	<2	<3	<4	<5	<6	<7	<8	<9	<10	17	Unknown
No. of cases ..	1	1	0	2	5	4	3	2	1	1	1	1

Age of Onset

All patients except one had their first spasm before the age of 10 months, and in fourteen it occurred between 4 and 8 months (table II). There is general agreement that the onset is usually within the 1st year of life, and is rare after 2 years.

Associated Mental Defect

All workers agree that severe mental deficiency is a common accompaniment of the spasms, often developing suddenly and simultaneously with their onset. While most workers do not specify the aspects particularly affected, Illingworth (1955) describes " intellectual " deterioration with preservation of motor functions. The gross and sudden deterioration in social responsiveness which he describes was seen in some of our cases, but it was accompanied in several patients by psychomotor retardation. Some of our patients, like his, were thought to have suddenly become blind. All except one showed some mental retardation when first seen at hospital. This was graded as gross (fifteen patients) or moderate (six patients):

Gross.—These patients were unable to hold up the head or fix the eyes, and several were thought by their parents to be blind. They responded infrequently or not at all to social overtures, and are best described as complete aments.

Moderate.—Although not complete aments, these patients were definitely retarded.

The patient (case 22) with normal mentality at the first visit (aged 17 months, 1 week after the first spasm) showed a gradual regression over the next 3 months, so that now at the age of 3 years she is moderately retarded.

The type of spasm bore no obvious relation to the degree of mental defect (table I).

TABLE I—CLINICAL FEATURES IN TWENTY-TWO CASES OF INFANTILE SPASMS

Case no.	Prenatal or perinatal factor	Age of onset of spasms (mos.)	Mental development before first spasm	Type of spasm	Mental retardation	Physical abnormality
(A) History of Probable Cerebral Damage:						
1	Breech, forceps, difficult labour; ill for 10 days (oxygen)	5	Slow	Flexor	Gross	Microcephaly, spasticity
2	Forceps for obstructed labour, cord round neck; ill for 4 days	8	Slow	Extensor, head to rt	Gross	Cerebral atrophy, hemiparesis
3	Prolonged labour, face cyanosed; did not cry for several weeks	<1	Slow	Extensor, head to rt, rt leg flexed	Gross	Microcephaly, spasticity
4	Cyanosed, delay in onset of respiration	3	Normal	Extensor	Gross	Microcephaly
5	Cæsarean section for slow growth; placental infarction; cerebral irritation, neonatal anoxia (B.W. 4 lb. 4 oz.)	5	Slow	Extensor, rt>lt	Moderate	Hypotonia, cataracts
6	Premature (B.W. 4 lb. 4 oz.); delay in onset of respiration; neonatal cyanotic attacks	4	Slow	Flexor	Gross	None
7	Premature (B.W. 3 lb.), breech; incubator 4 weeks	7	Slow	Extensor	Gross	Microcephaly, spasticity
8	Thrombocytopenic purpura at birth; neonatal thrush œsophagitis with incoordination of swallowing	5	Doubtful	Flexor	Gross	Hydrocephalus
(B) History of Possible Cerebral Damage:						
9	Forceps delivery, full term; normal neonatal period	6	Normal	Flexor	Gross	Hypotonia
10	Forceps delivery, full term; " head bruised "	9	Slow	Flexor	Moderate	None
11	Cæsarean section at 36 weeks for toxæmia (B.W. 5 lb. 10 oz.)	5	Slow	Flexor	Gross	None
(C) No History of Cerebral Damage:						
12	None	7	Slow	Extensor	Gross	None
13	None	4	Doubtful	Flexor	Gross	None
14	None	1	?	Flexor	Gross	None
15	None	Unknown	Doubtful	Flexor	Gross	None
16	None	6	Normal	Extensor	Moderate	None
17	None	6	Normal	Flexor	Moderate	None
18	None	3	Normal	Flexor	Gross	None
19	None	4	Normal	Flexor	Moderate	None
20	None	4	Normal	Flexor	Gross	None
21	None	4	Normal	Flexor	Moderate	None
22	None	17	Normal	Flexor	None	None

Associated Physical Abnormality

This is uncommon but not exceptional. Generalised spasticity occurred three times, hemiparesis once, hydrocephalus once, and severe hypotonia twice. There were four patients with microcephaly. Table I shows that physical abnormalities were usually associated with a history suggesting prenatal or perinatal brain injury. Hess and Neuhaus (1952), Gibbs and Gibbs (1952), Gastaut and Roger (1953), and Thiébaut et al. (1955) found various abnormal neurological signs in some, but not all, cases.

Ætiology

For several reasons it seems justifiable to consider prenatal or perinatal brain damage (including anoxia) or maldevelopment as important factors in the genesis of infantile spasms in some cases. Group *A* in table I consists of eight cases in whom cerebral damage at or before birth seems probable from the history. This is supported by the presence in all except one of physical abnormalities which could have resulted from such damage, whereas there were no abnormalities in the eleven patients of group *C*, where pregnancy, birth, and the neonatal period were normal. Again, at least six of those in group *A* had shown evidence of mental retardation before the first spasm, compared with only one in group *C*.

We feel, therefore, that there are reasonable grounds for implicating prenatal or perinatal brain damage as the cause in at least eight of our cases. In the three other patients (group *B*) where prenatal or perinatal brain damage may have occurred, the history is so indefinite that no conclusion as to its relevance can be reached.

In the eleven patients in group *C* no clue to ætiology could be found in the history, examination, or investigations. Only one child had a family history of epilepsy. The suggestion of Baird and Borofsky (1957) that diphtheria or pertussis immunisation might be relevant seems unlikely to apply to our patients since seven of them had not been immunised against either disease. Unfortunately we do not know the time relationship between immunisation and onset of spasms in the other four cases, but it is unlikely to be short since immunisation was not mentioned by any parent. Illingworth (1958) and Livingston et al. (1958) also found no evidence to confirm this suggestion. Skull radiographs, urine tests for phenylketonuria and aminoacid, sugar chromatograms, and E.E.G.s (which are considered below) were unhelpful. Pneumoencephalography was not performed as it has been non-contributory in previous investigations, showing either a normal appearance or ventricular dilatation (Zellweger 1948, Vasquez and Turner 1951, Thiébaut et al. 1955, Livingston et al. 1958).

From this and previous studies there seems no doubt that infantile spasms can be associated with organic cerebral disorder, and particularly birth injury. Zellweger (1948) alone found no correlation with birth injury. Unlike Gibbs et al. (1954) we did not obtain a history of encephalitis in any of our cases. All workers agree that in about half the patients no ætiological factor can be discovered by present methods. This group is at once fascinating and pitiable. A previously normal child is suddenly struck by a devastating but unknown agent, which usually causes severe and irreversible mental deficiency as well as infantile spasms. (Possibly the first spasm causes the mental deficiency from anoxia; but we agree with Illingworth [1955] that this seems unlikely, for the spasm is brief and significant apnœa could hardly occur.) Discovery of the cause seems as far away as it was in West's day.

Treatment

Routine anticonvulsant therapy has been as disappointing in our patients as in those of others (Gibbs et al. 1954, Illingworth 1955, Chao et al. 1957, Baird and Borofsky 1957, Livingston et al. 1958). Chlortetracycline (Stamps et al. 1951, Gibbs et al. 1954) produced a temporary remission or reduction in the number of spasms in five patients, and in one other the remission was permanent (case 21); this was the only patient who showed mental improvement after its administration. We have used pyridoxine (Livingston et al. 1955) in three children with no effect. Corticotrophin and cortisone have been used recently (Sorel and Dusaucy-Bauloye 1958, Low 1958), and initial results are promising.

Prognosis

All workers agree that most patients remain mentally defective although the spasms diminish in frequency or disappear. A few die within a few years of the onset of spasms.

We shall say little about prognosis because our follow-up is as yet short. Of our twenty-two patients two have died. The remainder remain mentally retarded, with one exception. This child (case 21) had a normal birth and neonatal history, and developed normally until 4 months when she had her first salaam spasm. The spasms were typical and moderate mental regression occurred. Chlortetracycline aborted the attacks, and after the age of 8 months they ceased. Now at $2^3/_4$ years she seems normal in every way. But unfortunately most of our patients remain pathetically unchanged as idiots or imbeciles—" a burden of hopeless pity to those who care for them " (*Lancet* 1956).

Illustrative Case-records

Case 19.—A boy, born naturally at full term (birth-weight 8 lb. 2 oz.), progressed normally at first. He smiled at 2 months, and was holding his head up and noticing well at 4 months, when he started to have infantile spasms of the salaam type. A sudden jerk would occur, his head and arms coming forwards —the arms into the " embrace " position of the Moro reflex— and his legs flexing at the hips. This was followed by a cry. The cycle would be repeated twelve to fourteen times. At first these bouts numbered thirty a day, but over the next 18 months their frequency diminished to about three a day. They became less severe, and at 22 months they comprised merely a nodding of the head and forward twitch of the shoulders which could easily escape notice.

When the salaam spasms started there was mental regression affecting social responsiveness more than motor abilities. The infant stopped smiling, responded poorly to social overture, and was thought to be blind. He started to walk with support at 11 months, but was ataxic until 17 months when he first walked alone. He would grasp with one hand at 12 months, and transfer an object from one hand to the other at 20 months. He could pronounce two words at 15 months, and his vocabulary had not increased by 22 months.

Case 6.—This child, born prematurely (birth-weight 4 lb. 4 oz.), did not breathe for 35 minutes, and had several cyanotic attacks in the neonatal period. He never smiled or noticed his mother. At 4 months he started to have sudden flexion movements of the trunk, repeated about ten times with a cry between the spasms, so that his mother thought he had abdominal pain. When first seen at hospital at 6 months, he was taking no notice of his surroundings; he failed to respond to light or to social overture, and showed poor head control. Muscle tone was normal. The limb reflexes were exaggerated symmetrically. He moved all limbs well. He has made no

progress since then, and now, at the age of $2^1/_2$ years, is a complete ament. He appears to be blind, has poor head control, cannot sit, and lies grimacing and making purposeless movements with all the limbs. He shows extreme hyperacusis. The spasms have been resistant to the usual anticonvulsants and to chlortetracycline, but they are now less frequent.

Case 12.—This baby, delivered normally at full term, sucked normally, but did not smile or take notice of his surroundings until 6 months. He could not raise his head from the pillow at 7 months, when he first attended hospital. At this time he had had spasms for 1 week; his arms would fly up beside his head with fists clenched, his head go backwards, his eyes turn upwards, and his thighs flex. The spasms lasted only a few seconds, but would be repeated as many as twelve times. Examination showed a mental retardation with no specific features. There was generalised hypotonia.

Chlortetracycline brought about cessation of the spasms for a week only, and anticonvulsants were ineffective. There was a slow deterioration in his mental level, and from the age of 18 months he was a complete ament. The spasms became less frequent, and his hypotonia changed to a generalised spasticity. He died at home at the age of $2^3/_4$ years.

Electroencephalographic Features

The definition of hypsarrhythmia given by Gibbs and Gibbs (1952) is as follows:

"very high voltage, random, slow waves and spikes in all cortical areas. The spikes vary from moment to moment in duration and location, at times they seem to be focal in one part of the cortex, and a few seconds later they seem to come from another focus, or possibly from multiple foci. Occasionally the spike discharge is generalised but it is never rhythmically repetitive or highly organised as in petit mal or petit mal variant. The chaotic appearance of this abnormality gives the impression of a nearly total disorganisation of cortical voltage regulation."

This pattern has been described under various names by American and European workers: slow spike-and-wave (Lennox and Davis 1950), type-B myoclonus (Gastaut and Rémond 1952), *diffuse gemischte Krampfpotential* (Hess and Neuhaus 1952), *dysrhythmie majeure de la première enfance* (Gastaut and Roger 1953).

Our investigation to establish the degree of correlation between infantile spasms and hypsarrhythmia is summarised below; the details are to be published elsewhere (Jeavons and Bower 1959).

From 3000 E.E.G. records of children under the age of 6 years taken at All Saints' Hospital and the Children's Hospital between 1954 and 1958, we selected those with a hypsarrhythmic pattern and those of children with infantile spasms regardless of their E.E.G. pattern. Only the first records of children aged 18 months or less at the time of recording were considered; there were 32 of these. For comparison we examined 24 first records of children in the same age-group with definite epilepsy other than infantile spasms and febrile convulsions.

A scoring system was used to separate the characteristics of hypsarrhythmia from those of epilepsy. The score was weighted so that utterly chaotic records (fig. 1) received maximum marks and highly organised epileptic records (fig. 2) received minimum marks.

Using this system we found that, although all except one of the children with infantile spasms had an abnormal record, only half the records (16 out of 32) showed the utterly chaotic picture of hypsarrhythmia as defined above; the other half showed a more organised epileptic pattern with centrencephalic or focal localisation. By contrast, 14 of the 24 records of children with epilepsy (not infantile spasms or febrile convulsions) had a normal E.E.G., and only 2 of the abnormal E.E.G.s showed hypsarrhythmia. We therefore conclude that a child with infantile spasms is very likely to have an abnormal first E.E.G. if this is taken before the age of 19 months, but there is an equal chance that it will be hypsarrhythmic or epileptic (centrencephalic or focal). A child in the same age-range with epilepsy (other than infantile spasms) is unlikely to have a hypsarrhythmic first record.

These findings are in partial agreement with those of others. It is generally concluded (Hess and Neuhaus 1952, Gastaut and Roger 1953, Gibbs et al. 1954) that the E.E.G. of patients with infantile spasms is usually abnormal (426 of 450 records, according to Burnett et al. 1958), but the abnormality is described as hypsarrhythmia by most workers. Hess and Neuhaus (1952) agree with us, however, that "mixed diffuse seizure discharge" (equivalent to the hypsarrhythmia of Gibbs and Gibbs 1952) is often absent and more focal epileptic records are found instead. E.E.G. examination is nevertheless a useful investigation where infantile spasms are suggested by the history but not witnessed. A normal E.E.G. is strong evidence against the diagnosis, while the presence of hypsarrhythmia is very much in favour of it.

We found no correlation between the presence of hypsarrhythmia and the type of spasm (i.e., whether flexor or extensor) or the degree of mental defect. Brain

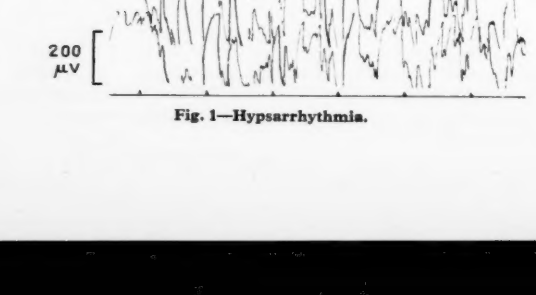


Fig. 1—Hypsarrhythmia.

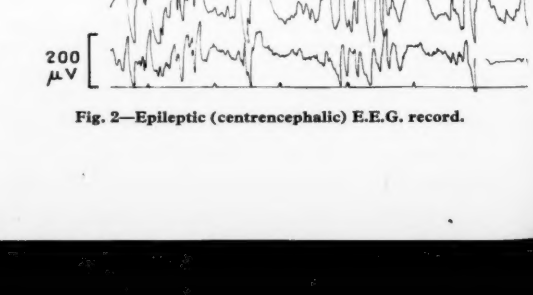


Fig. 2—Epileptic (centrencephalic) E.E.G. record.

damage at or before birth was more frequently associated with an epileptic record than a hypsarrhythmic one.

Incidence of Infantile Spasms and Hypsarrhythmia

Owing to the variety of names given to the clinical and E.E.G. patterns, it is difficult to assess the incidence accurately from published reports. The conditions appear to be rare.

Zellweger (1948) described thirty-two cases of infantile spasms seen between 1928 and 1948, and he collected sixty-two cases from the world literature up to 1948. Lennox and Davis (1950) described thirty-seven cases, Vazquez and Turner (1951) ten, Gastaut and Roger (1953) thirty-five, and Hess and Neuhaus (1952) fifty-five. Burnett, Gibbs, and Gibbs (1958), on the other hand, have now seen four hundred and fifty. Presumably these have come from a wide area because of the authors' well-known interest in the condition. In this country Illingworth (1955) saw twelve patients with sudden mental deterioration and infantile convulsions in 7 years. Many of these workers described hypsarrhythmic E.E.G. patterns in their cases. In addition Thiébaut et al. (1955) described twenty-five patients with hypsarrhythmia, and Baird and Borofsky (1957) found 80 hypsarrhythmic records in 2000 E.E.G.s taken over a 5-year period.

Our first cases were seen in 1954; and the number has increased recently, probably because in 1956 we asked all pædiatricians in the Birmingham Region to refer children with infantile spasms to one of our E.E.G. departments. The number referred in the 2 years from January, 1956, was twenty-nine. This probably represents most of the cases, since the dramatic nature of the condition is likely to lead to referral to a pædiatrician. The estimated number of children under 6 years of age in the region was 148,000 in 1957. Infantile spasms therefore seem to be rare in this area, and hypsarrhythmia even rarer.

Summary

The clinical features of twenty-two patients with infantile spasms are described.

This rare form of epilepsy usually starts at about 6 months of age. The spasm is generalised, rapid, and brief, and may be flexor or extensor. It may be followed by a cry, and is often repeated to form a series. Definite mental retardation, often severe, is almost invariably associated with it.

In about half the cases there is a history of prenatal or perinatal cerebral damage, and in these cases mental development is usually retarded from birth. Physical abnormalities may be found in this group. In the other half the ætiology is unknown, and in these children mental development is usually normal up to the time of the first spasm.

Anticonvulsants do not usually inhibit infantile spasms, but chlortetracycline may temporarily do so.

A few patients die early. Improvement in mentality is unlikely in the survivors.

In patients with infantile spasms the electroencephalogram (E.E.G.) is almost always abnormal, but definite hypsarrhythmia is found in only half of the first records; the others show an epileptic abnormality, which is often severe. By contrast, more than half the patients with epilepsy (not infantile spasms) in the same age-group have a normal E.E.G., and a hypsarrhythmic record is rare. Although a non-hypsarrhythmic, epileptic record may be found in patients with infantile spasms, E.E.G. examination of suspected cases is very useful; for a normal record is strongly against the diagnosis, while a hypsarrhythmic one is very much in favour of it.

We wish to thank Prof. J. M. Smellie for his encouragement and help in this study; the consultant physicians at the Children's Hospital and the consultant pædiatricians in the Birmingham Region, especially Dr. A. C. Kendall, for their cooperation and interest; and Mrs. Trilloe, Miss D. J. Campbell, Miss M. E. Dyas, and Miss A. E. Hill, the recordists at the two hospitals, for their patience and skill in performing E.E.G. examinations on these difficult patients.

REFERENCES

Asal, B., Moro, E. (1924) *Jb. Kinderheilk.* **107**, 1.
Baird, H. W., Borofsky, L. G. (1957) *J. Pediat.* **50**, 332.
Bridge, E. M. (1949) Epilepsy and Convulsive Disorders in Children. New York.
Burnett, L. L., Gibbs, E. L., Gibbs, F. A. (1958) *Pediatrics, Springfield*, **21**, 719.
Chao, D. H., Taylor, F. M., Druckman, R. (1957) *J. Pediat.* **50**, 670.
Gastaut, H. (1954) The Epilepsies. Springfield, Ill.
— Rémond, A. (1952) *Rev. neurol.* **86**, 596.
— Roger, A. (1953) *Pédiatrie*, **8**, 605.
Gibbs, E. L., Fleming, M. M., Gibbs, F. A. (1954) *Pediatrics*, **13**, 66.
Gibbs, F. A., Gibbs, E. L. (1952) Atlas of Electroencephalography; vol. II. Cambridge, Mass.
Hess, R., Neuhaus, T. (1952) *Arch. Psychiat. Nervenkr.* **189**, 37.
Illingworth, R. S. (1955) *Arch. Dis. Childh.* **30**, 529.
— (1958) *in* Year Book of Pediatrics (edited by S. S. Gellis); p. 399. Chicago.
Jeavons, P. M., Bower, B. D. (1959) *Electroenceph. clin. Neurophysiol.* (in the press).
Lancet (1956) i, 561.
Lennox, W. G. (1945) *J. Amer. med. Ass.* **129**, 1069.
— Davis, J. P. (1950) *Pediatrics*, **5**, 626.
Livingston, S., Eisner, V., Pauli, L. (1958) *ibid.* **21**, 916.
— Hsu, J. M., Petersen, D. C. (1955) *ibid.* **16**, 250.
Low, N. L. (1958) *ibid.* **22**, 1165.
Pond, D. A. (1958) *in* Modern Trends in Pædiatrics (edited by A. Holzel and J. P. M. Tizard). London.
Sorel, L., Dusaucy-Bauloye, A. (1958) *Acta neurol. belg.* **58**, 130.
Stamps, F. W., Gibbs, E. L., Haase, E. (1951) *Dis. nerv. Syst.* **12**, 227.
Thiébaut, F., Sacrez, R., Röhmer, F., Isch-Treussard, C. (1955) *Rev. neurol.* **93**, 455.
Vasquez, H. J., Turner, M. (1951) *Arch. argent. Pediat.* **35**, 111.
West, W. J. (1841) *Lancet*, i, 724.
Zellweger, H. (1948) *Helvet. pædiat. acta*, **3** (suppl. 5), 141.

DIETARY TREATMENT OF AN INFANT WITH PHENYLKETONURIA

F. S. W. BRIMBLECOMBE
M.D. Lond., M.R.C.P., D.C.H.
CONSULTANT PÆDIATRICIAN, EXETER CITY HOSPITAL

MARGARET E. R. STONEMAN
M.B. Manc., D.C.H.
PÆDIATRIC REGISTRAR, EXETER CITY HOSPITAL

R. MALIPHANT
B.A. Lond., Dip Psych.
LATE ASSISTANT EDUCATIONAL PSYCHOLOGIST, DEVON COUNTY COUNCIL

THE intelligence of most infants with phenylketonuria deteriorates rapidly in the first months of life (Woolf et al. 1958). Tests of development using the Griffiths (1954) scale indicate that by the age of 12 months a state of idiocy has usually been reached and that subsequently the mental deterioration continues but at a slower rate. Very rarely in an untreated case the infant retains normal or near normal intelligence (Armstrong and Tyler 1955).

Drastic restriction of dietary phenylalanine can reduce the abnormally high blood-level of this aminoacid to normal (Blainey and Gulliford 1956, Hsia et al. 1958), but the effect of such treatment on the intellect of these patients varies greatly with the age at which treatment is started (Woolf et al. 1958). All the available evidence suggests that, if dietary treatment alone is to have any notable effect upon the eventual intelligence of these patients, then such treatment must be started before intelligence has deteriorated seriously: in other words its value seems to lie more in the prevention of intellectual deterioration than in the correction of established mental deficiency, although some slight and often worth-while improvement in intelligence may be expected.

When dietary treatment has been started in the first months of life it is difficult to prove that this has prevented mental deficiency in an individual infant, because 1% of

untreated patients (Penrose 1951) have an intelligence quotient above 70. This reservation applies to the patient treated from the age of a few weeks by Horner and Streamer (1956) and to a similar patient treated by Woolf et al. (1958). Thus, although the present evidence is highly suggestive, the value of early treatment can be finally proved only when a significant number of infants have been adequately treated from a very early age.

We wish to record the progress of an infant in whom minor intellectual deterioration had apparently started when treatment was initiated, and in whom there is highly suggestive evidence of recovery and maintenance of normal intelligence over a two-year period of treatment.

Case-record

A male infant, born on Nov. 11, 1955, was the first child of healthy parents between whom there was no consanguinity. He first came under our care at the age of 4 weeks suffering from both infantile pyloric stenosis and gastroenteritis. After a successful Rammstedt's operation he was transferred to an isolation hospital for treatment of his gastroenteritis. Subsequently his weight gain was not entirely satisfactory, and for this reason he was transferred back to our care at the age of 10 weeks.

Shortly after his readmission the ward staff-nurse commented that he was taking little interest in his surroundings, failing to smile, and making little attempt to move his head. On account of her observation his urine was tested and was found to contain phenylpyruvic acid. Subsequently the diagnosis was confirmed by the finding of phenylalanine in the urine by chromatography. Blood-phenylalanine estimations were not carried out before treatment.

Dietary restriction of phenylalanine was started at the age of 17 weeks along lines similar to those advocated by Woolf et al. (1955). The urine soon became free of phenylketones as shown by the ferric-chloride test; but the level of dietary phenylalanine was at this time consistently above 25 mg. per kg. body-weight daily, and the infant's rate of development (Griffiths scale) continued to deteriorate (fig. 1).

When normal weaning time arrived, the choice of diet for this child became very difficult; but with the help of Dr. W. F. J. Cuthbertson an entirely new feeding schedule was

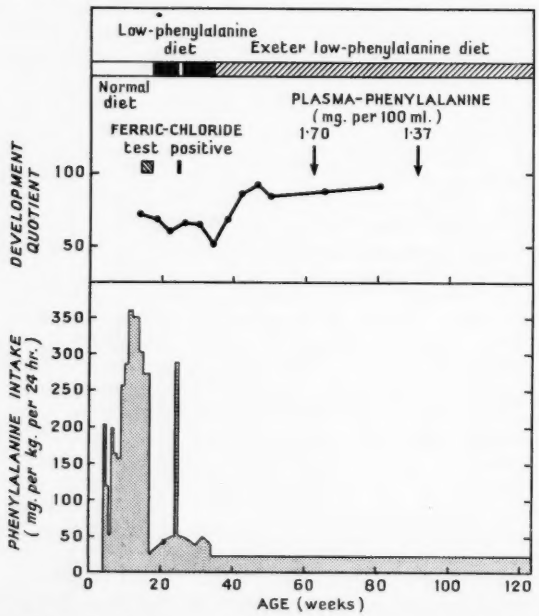


Fig. 1—Development quotient related to dietary phenylalanine.

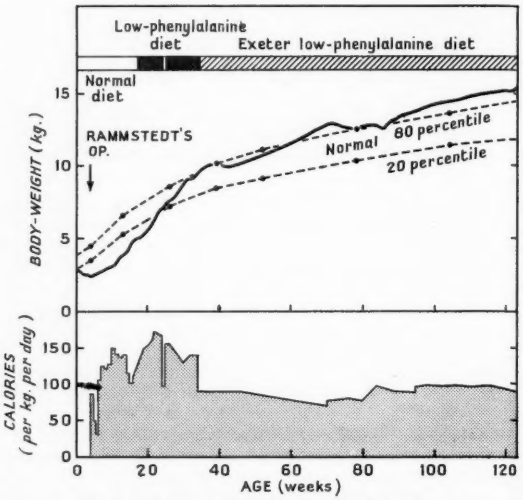


Fig. 2—Body-weight related to calorie intake.

Values for weights of normal children, indicated as 80 percentile and 20 percentile curves, are from Falkner (1958).

devised. Every effort was made to make the diet as varied and as palatable as possible. The new diet was started when the child was 34 weeks old, since when his dietary phenylalanine has been restricted to approximately 25 mg. per kg. daily, and his calorie intake to 75–100 calories per kg. daily. His dietary tryptophan has been similarly maintained at approximately 25 mg. per kg. daily, and tyrosine at approximately 50 mg. per kg. daily.

In the two and a half years of dietary treatment so far completed these fixed restrictions have necessitated frequent modifications of diet, not only on account of the increase in the child's total requirements, but also in view of the normal transition first to a weaning diet and later to more solid food. The first solid foods introduced into the diet (at 34 weeks) were egg, meat, potatoes, and oatmeal porridge in extremely small amounts. Subsequently the inevitable increase in the total bulk of food required has necessitated replacement of some of these ingredients by other foods with a lower phenylalanine content. His diet at present includes small helpings of cereals, meat, and fish, and more generous helpings of vegetables, fruit, and specially prepared bread or biscuits made from wheat-starch flour and vegetarian margarine. The casein hydrolysate of low phenylalanine content which is required to maintain a normal protein intake is given in tomato or fruit juice. Knowledge of the phenylalanine and tryptophan content of foods is incomplete. We accepted the opinion of Dr. B. P. Hughes, who estimates a possible error of 5–10% in the content of these aminoacids in the diet provided for this patient.

He was discharged home on April 21, 1956, at the age of 22 weeks, since when his mother has been responsible for preparing his food. The consistently negative ferric-chloride test on his urine and the normal blood-level of phenylalanine on the three occasions on which it has been estimated give proof of her efficiency in following instructions. There has been little difficulty in persuading the infant to take his special diet, and throughout the two and a half years' treatment his weight gain has been satisfactory (fig. 2).

Psychological Assessment

This child has had fifteen assessments of his mental development, the first at the age of 14 weeks. The Griffiths mental development scale was used for the first twelve examinations. The Revised Stanford-Binet intelligence scale (form L) and the Merrill-Palmer performance scale were used for the last three assessments.

Fig. 1 indicates the rate of mental development using the Griffiths development quotient. The more rapid rate of

development after the sixth assessment (chronological age 34 weeks) is very distinct. It was shortly before this assessment that the child was changed from his original low-phenylalanine diet to the more rigidly controlled diet on which he has been subsequently maintained. He was able to sit unsupported at the age of 38 weeks, pull himself to a standing position at 46 weeks, crawl (only in reverse!) at 50 weeks, and walk alone and say 4 or 5 words at 81 weeks. Assessments using the Merrill-Palmer and the Revised Stanford-Binet scales from the age of 2 years indicate that his intelligence is now within the range of normal. It would appear unlikely that such an improvement could be entirely attributed to his having gone home from hospital. The parents had maintained close contact with the child while in hospital, and none of the adverse symptoms sometimes noticed in children separated for long periods from their parents were reported by the mother or observed by the psychologist.

In summary, the earlier assessments using the Griffiths scale supported the observation of the staff-nurse who had in the first instance suspected some retardation in development at the age of 14 weeks; while the most recent assessments—and particularly those at the age of 2 years—show that this child is now within the normal range of intellectual and physical development.

Discussion

This child has been treated on a diet in which both phenylalanine and tryptophan are restricted to approximately 25 mg. per kg. body-weight daily. From our experiences with three other patients under treatment, and from the work of J. R. Squire and J. D. Blainey (personal communication), it seems probable that this level of restriction may be insufficient in some cases to reduce the blood-level of phenylalanine to normal. Clearly in each individual case dietary restriction of phenylalanine should be so regulated as to maintain the blood-level of phenylalanine within normal limits. We consider that an important factor, stressed by Prof. J. R. Squire (personal communication), has been the maintenance of a high-carbohydrate high-calorie intake in order to discourage endogenous metabolism of protein, which might give rise to accumulation of phenylalanine in the plasma.

The associated restriction of dietary tryptophan to approximately 25 mg. per kg. daily has not interfered in two and a half years with this child's weight gain and general nutrition, but we cannot yet evaluate its effect on his rate of mental development.

Studies of affected siblings of known cases (Armstrong and Binkley 1956) indicate that the blood-level of phenylalanine may begin to rise between the second and sixth weeks of life; and dietary restriction should be started as soon as possible. We agree with Woolf et al. (1958) that all infants should have their urine tested for phenylketones at the age of 3 weeks, but suggest that this test should be repeated at 6 weeks.

Summary

Normal intelligence was apparently regained and maintained in a child with phenylketonuria, in whom dietary treatment was started at the age of 17 weeks.

The evidence suggests that treatment must be started at a very early age if the rate of mental development is to be notably enhanced. All infants should have their urine tested for phenylketones at the age of 3 weeks, and possibly again at 6 weeks.

Our thanks are due to Professor J. R. Squire for advice and encouragement; to Dr. J. D. Blainey for carrying out the estimations of blood-phenylalanine and to Miss Margaret M. MacCready, B.Sc., for carrying out the chromatographic examinations of the urine; to Dr. W. F. J. Cuthbertson, of Glaxo Laboratories, for his help in planning the initial stages of the diet; to Dr. A. S. Fairbairn, of the Statistical Research Unit, London School of Hygiene, for his criticism of the statistical data; to Dr. B. P. Hughes, of the Medical Research Council department of experimental medicine, University of Cambridge, for his advice concerning the aminoacid content of various food-stuffs; and finally to Staff-Nurse E. Luscombe for her acute observation.

REFERENCES

Armstrong, M. D., Binkley, E. L. (1956) *Proc. Soc. exp. Biol., N.Y.* **93**, 418.
— Tyler, F. H. (1955) *J. clin. Invest.* **34**, 565.
Blainey, J. D., Gulliford, R. (1956) *Arch. Dis. Childh.* **31**, 452.
Falkner, F. (1958) *ibid.* **33**, 1.
Griffiths, R. (1954) The Abilities of Babies. London.
Horner, F. A., Streamer, C. W. (1956) *J. Amer. med. Ass.* **161**, 1628.
Hsia, D. Y. Y., Knox, W. E., Quinn, K. V., Paine, R. S. (1958) *Pædiatrics*, **21**, 178.
Penrose, L. S. (1951) *Ann. Eugen., Camb.* **16**, 134.
Woolf, L. I., Griffiths, R., Moncrieff, A. A. (1955) *Brit. med. J.* i, 57.
— — — Coates, S., Dillistone, F. (1958) *Arch. Dis. Childh.* **33**, 31.

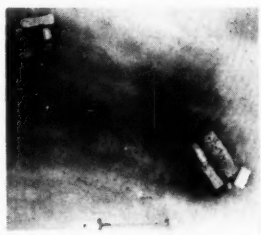
Preliminary Communication

ENHANCING EFFECT OF CRYSTALLINE PHOSPHOLIPID FROM HUMAN BREAST TUMOUR ON NEOPLASMS IN ANIMALS

THE antigenicity of tumour phospholipids [1 2] led me to study the biological activity of these phospholipids and their effect on tumour growth. The work reported here was carried out with phospholipids obtained from human breast tumours.

The phospholipids were extracted,[1] purified by repeated extraction with chloroform, and crystallised by differential temperature salting out [3] at 0–2°C.

The effect of these tumour phospholipids on the growth of spontaneous mammary tumour in mice and on the growth of 1, 2, 5, 6-dibenzanthracene (D.B.A.) transplantable rat carcinoma was studied in vivo:



Crystalline phospholipids from human breast tumour after recrystallisation. (×1000.)

1. Twenty-five mice with spontaneous mammary tumour (approximate size 0·5 × 0·5 cm.) were injected intravenously twice weekly with 0·2 ml. of 1% solution of the phospholipids in physiological saline solution (treated). A second group of twenty-five mice with tumours of similar size were injected with 0·2 ml. of physiological saline solution twice weekly (controls).

2. Fifty rats with D.B.A. transplantable rat carcinoma (approximate size 1·0 × 1·0 cm.) were injected intravenously, twice weekly, with 0·4 ml. of 1% solution of the phospholipid in physiological saline solution (treated); a second group of fifty rats with D.B.A. transplantable tumours of similar size were injected with physiological saline solution only (controls).

The accompanying figure shows the crystalline phospholipids after three-times recrystallisation. The growth

TABLE I—NUMBER OF ANIMALS SURVIVING AT DIFFERENT TIMES (DAYS) AFTER TREATMENT WITH CRYSTALLINE PHOSPHOLIPIDS

Days after treatment	Mice with spontaneous mammary tumours		Rats with D.B.A. transplantable carcinoma *	
	Control	Treated	Control	Treated
2	25	23	50	50
8	23	18	49	48
15	20	10	45	20
22	18	2	44	15
30	3	0	42	5
40	0	0	40	2

* In 30 of the 40 rats alive after 40 days the tumours were regressing.

1. Hakim, A. A. *Clin. chim. acta*, 1957, **2**, 560.
2. Hakim, A. A. *Exp. Med. Surg.* 1956, **14**, 211; *ibid.* 1957, **15**, 222; *Proc. Amer. Ass. Cancer Res.* 1956, **2**, 113.
3. Hakim, A. A. *Naturwissenschaften* (in the press).

TABLE II—EFFECT OF PHOSPHOLIPID FROM HUMAN BREAST TUMOUR ON SIZE (CM.) OF D.B.A. TRANSPLANTABLE TUMOURS IN RATS

Group	Days after start of treatment	Rat no.						
		1	2	3	4	5	6	7
Control	2	1·0 × 0·9	1·1 × 0·8	1·0 × 1·2	1·3 × 1·2	1·0 × 1·0	0·9 × 0·8	1·0 × 0·9
	5	1·8 × 1·3	2·6 × 1·3	2·2 × 1·4	1·6 × 1·4	1·0 × 1·4	1·8 × 1·2	1·5 × 1·2
	11	3·2 × 1·2	4·6 × 1·9	5·0 × 1·6	4·9 × 1·6	4·0 × 1·6	4·0 × 2·8	4·6 × 1·6
	14	6·0 × 2·2	6·5 × 2·2	5·2 × 3·0	7·2 × 3·8	6·0 × 3·2	5·1 × 2·0	4·8 × 3·6
	17	6·8 × 2·8	6·0 × 2·4	6·0 × 3·2	7·6 × 4·0	6·6 × 3·8	6·2 × 3·5	5·9 × 4·0
	21	7·5 × 3·2	6·3 × 2·8	6·4 × 3·4	8·0 × 4·0	6·9 × 4·2	6·8 × 4·0	6·6 × 4·7
	24	7·8 × 3·6	7·0 × 3·0	6·6 × 3·6	8·3 × 4·5	7·5 × 4·3	7·0 × 4·0	7·2 × 5·0
	28	8·0 × 3·8	7·5 × 3·2	7·0 × 3·8	Died	7·9 × 5·2	7·5 × 4·3	7·6 × 5·3
	32	Died	7·8 × 3·5	7·5 × 4·0	..	8·0 × 5·6	8·0 × 4·6	Died
	34	..	Died	7·7 × 4·2	..	Died	Died	..
	36	..	..	Died	..	..	..	..
Treated	2	1·2 × 1·3	0·9 × 1·0	1·1 × 1·2	1·0 × 0·9	1·2 × 0·9	1·0 × 1·1	1·2 × 0·9
	5	3·6 × 1·8	3·5 × 2·2	3·0 × 2·4	3·0 × 1·8	2·0 × 1·0	3·5 × 1·8	3·9 × 2·0
	11	8·1 × 2·6	7·3 × 3·0	6·6 × 3·4	6·4 × 3·0	6·5 × 2·0	6·6 × 2·6	6·9 × 3·0
	14	8·4 × 4·8	8·2 × 3·6	7·5 × 4·2	7·0 × 3·8	7·4 × 3·0	7·5 × 3·6	7·8 × 4·2
	17	Died	8·3 × 4·9	8·0 × 4·6	8·9 × 4·0	7·8 × 3·9	8·2 × 4·0	8·5 × 5·3
	18	..	Died	Died	Died	Died	Died	Died
	21	..	..	..	..	..	..	..

of tumours proceeded faster in the treated animals than in the controls. Table I shows the numbers of rats surviving at different times after treatment, and table II shows serial estimations of tumour size in seven control and seven treated rats.

A group of ten normal rats (with no transplantable carcinoma) were injected intravenously with 0·4 ml. of 1% solution of the crystalline tumour phospholipid in physiological saline solution twice weekly for five weeks. All ten rats remained alive; no apparent signs of tumour development or of hæmorrhage were noted. The solutions of the phospholipids produced no signs of toxicity in normal mice injected with similar doses (i.e., 0·2 ml. twice weekly).

Following our extraction procedure, a tumour-enhancing factor was demonstrated in crude phospholipids obtained from animal tumours.[4] Both a water-soluble [5] and fat-soluble [6] factor have been reported. Studies on crystalline phospholipids from other types of human tumour are in progress.

Biochemistry Research Laboratories,
Miami Heart Institute,
4701, North Meridian Avenue,
Miami Beach 40, Florida, U.S.A.

ANWAR A. HAKIM
PH.D. Geneva

4. Green, H. N., Wilson, R. *Nature, Lond.* 1956, **178**, 851.
5. Kaliss, N. *Ann. N.Y. Acad. Sci.* 1955, **59**, 385.
6. Martinez, C., Miroff, G., Bittner, J. J. *Cancer Res.* 1955, **15**, 442.

Reviews of Books

Non-toxaemic Hypertension in Pregnancy

Editors: NORMAN F. MORRIS, M.D., M.R.C.O.G., professor of obstetrics and gynæcology, University of London; J. C. MCCLURE BROWNE, B.SC., M.B., F.R.C.S.E., F.R.C.O.G., professor of obstetrics and gynæcology, University of London. London: J. & A. Churchill. 1958. Pp. 243. 35*s*.

THIS book reports faithfully and in detail a symposium held at Hammersmith Hospital in July, 1957, and attended by obstetricians, physicians, and statisticians. The less common causes of non-toxæmic hypertension, such as phæochromocytoma, primary renal disease, and coarctation of the aorta are given space in proportion to their incidence, and the greater part of the book is devoted to the effect of essential hypertension on the pregnant mother and her fœtus. It is made abundantly clear that obstetricians rightly consider certain blood-pressures, which the physician would consider normal or near-normal, as of grave significance to the pregnant woman. Although many consider a pressure of 140/90 the upper limit of normal, Professor McClure Browne presents unassailable evidence that women with pressures greater than 120/70 but less than 140/90 may develop toxæmia as readily as those whose initial pressure is 140/90 or more. In this connection Vartan's experience at Woolwich affirms the contention of McClure Browne's father, Prof. F. J. Browne, that the upper limit of normal blood-pressure in pregnant women is 130/70. Unless women with these lesser degrees of hypertension are recognised as being at risk, and unless they are watched carefully, they may have a higher incidence of pre-eclamptic toxæmia (39% in McClure Browne's series) and a higher fœtal wastage than those with an initial pressure of 140/90, who were specially supervised and in whom the incidence of pre-eclamptic toxæmia was 24%.

This book contains much of interest to all obstetricians, and to physicians particularly concerned with pregnant women. The details and statistics are essential to the research-worker, but the result makes for indigestible reading. Although the editors have presented the material admirably, they might perhaps have offered a 20-page summary of the many important points buried in the detailed papers, and so made the whole more attractive to the day-to-day obstetrician, who certainly has to read this book.

Industrial Health Technology

BRYAN HARVEY, M.A., M.SC., A.I.M.E.; ROBERT MURRAY, B.SC., M.B., D.P.H., D.I.H. London: Butterworth. 1958. Pp. 337. 45*s*.

THIS book has been written to inform industrial management, trade unions, and welfare workers about industrial health and hygiene. The authors are to be congratulated on compressing a vast amount of information into a small volume which should prove useful to all concerned in maintaining health in industry. The chapter on exhaust ventilation is excellent, and will be an invaluable practical guide to industrial medical officers and ventilation engineers. The toxicity of a wide range of organic and inorganic dusts and vapours and metallic fume is mentioned, together with the manifestations of poisoning. Finally, there is a section dealing with the comfort of the worker in which noise and optimum heat, lighting, and ventilation are discussed.

A Laboratory Manual on Abnormal Hæmoglobins (Oxford: Blackwell Scientific Publications. 1958. Pp. 39. 9*s*. 6*d*.).—An international symposium held in 1957 in Istanbul had as its subject the abnormal hæmoglobins. Associated with this meeting, held under the auspices of the C.I.O.M.S. and UNESCO, was a training course of which this manual, prepared under the direction of J. H. P. Jonxis and T. H. J. Huisman, is the outcome. It contains a brief résumé of the hæmoglobinopathies, their practical and theoretical importance, and methods required in their diagnosis. A third of the technical section is given to basic methods. The remainder deals with the preparation of hæmoglobin samples, the best way of shipping samples to specialist laboratories, the sickling test, paper and starch electrophoresis, cation-exchange chromatography, and the measurement of alkali denaturation (for the estimation of the alkali-resistant fœtal hæmoglobin). This manual will be welcomed by many laboratory workers.

THE LANCET

LONDON 21 MARCH 1959

The Future of Child Guidance

THE potential importance of child-guidance services can scarcely be overstated; for experiences in the early years, echoing throughout life, can also influence subsequent generations. Many believe that the activities of child-guidance clinics should be extended into the community, influencing teachers and parents in a truly prophylactic way. But at present our child-guidance service falls short of its responsibilities, and it badly needs more staff. Research has inevitably lagged: as Dr. LEO KANNER [1] has remarked, we are little better able to classify childhood psychosis now than was HENRY MAUDSLEY in 1860. Child psychiatry occupies an embattled intermediate position between several scientific and not-so-scientific disciplines, and between the Ministries of Health and Education and their multifarious representatives. The new Ministry of Education circular [2] is the latest link in a long complex chain of argument and recommendation.

The Ministry rightly seeks to plan ahead for its child-guidance services despite the present staff shortages, and it founds its recommendations largely on the advice of the Committee on Maladjusted Children, published in November, 1955.[3] Much of the circular rests on firm ground: for example, the intention to provide comprehensive services from preschool years to the age (presumably) of 18—the age stated in 1955 but not repeated here. The Ministry abandons its 1948 objective [4] of creating two types of clinic—a centre run by the regional hospital board dealing with iller children, in addition to the usual type which was meant to be "in the main an educational service". We gladly sing requiems over this corpse, for to expect two such organisations to coexist and refer cases to each other would be to add chaos to chaos. The present circular pictures the clinic staff leaving the clinic and taking a wide advisory role in child care and in the guidance of parents and teachers: sensible social prophylaxis such as this is worth while and necessary, though it takes much time. It does not cause the ethical complications which arise when, as the Ministry insists, the therapeutic services are directly accessible to parents. The psychology subcommittee of the British Pædiatric Association [5] doubted the advisability of this and the council of the British Medical Association [6] was emphatically opposed to it. Already cases can be referred by head teacher, educational psychologist, school medical officer, and hospital in addition to the family doctor (juvenile courts are not mentioned), although it is said that the family doctor should be consulted and receive reports. Will free access really help many parents? Will parents that take advantage of it be those most in need of help? Would it really make much difference to public attitude if the matter were talked over with the family doctor first, and might this not indeed help? Do clinic psychiatrists happily open their doors to all who come? If society really took to child guidance, the most elaborate service might be swamped; for what child does not at some time refuse its food and wake crying in the night? The selection of cases for therapy is not easy; but there is certainly much to be said for retaining the family doctor as the first line of defence.

The circular repeats many times the admirable, if platitudinous, intention that there should be full liaison between the numerous persons and organisations involved in child-guidance work. The recommended staff of psychiatrist, psychologist, and psychiatric social worker in the ratio of 1 : 2 : 3 is probably about right; but many will regret that the organisation will continue as before, with the clinic and staff provided by the education authority and the psychiatrist by the regional hospital board. This is alleged to secure the necessary cooperation between health and education services, but the B.M.A.[6] did not exaggerate in describing the tensions which result from it. Allied to this problem of mixed responsibility is the siting of future clinics: evidently these are to be located as hitherto in education-authority premises and to be related primarily to the educational services. At least since 1948 [7] it has been widely thought that child-guidance centres should be developed in close association with children's hospitals and pædiatric departments of general hospitals; and Dr. MILDRED CREAK [8] concludes that such an arrangement would end much of the present dissatisfaction among child psychiatrists isolated in space and thought from their colleagues both in psychiatry and in pædiatrics. The psychology subcommittee of the British Pædiatric Association in its later thoughts [5] agreed that there are serious disadvantages in basing the child-guidance clinics on the educational services, and recommended that they be rooted in the general hospitals; the B.M.A.[6] thinks similarly; and the Royal Medico-Psychological Association, while conceding that "joint" clinics can run smoothly, said that they have many drawbacks, and urged the steady development of child-psychiatry clinics, with or without inpatient units, in association with medical institutions.[9] In Northern Ireland the child-guidance service is apparently regarded as the responsibility of hospital and health authorities.[10] Clearly at a time when pædiatric facilities are underemployed to the point where whole hospitals are in the throes of seizure for other purposes, and when child-psychiatry clinics are flooded to the point of submersion, a link could benefit both. We believe that such integration would solve many problems, would facilitate research, and

1. *Lancet*, 1958, ii, 1108.
2. Circular 347, March 10, 1959.
3. H.M. Stationery Office, 1955. See *Lancet*, 1955, ii, 1328.
4. Ministry of Education circular 179, para. 18. Aug. 4, 1948.
5. Report to executive on Ministry of Health and Ministry of Education draft circulars and letters on child guidance, October, 1957.
6. *Brit. med. J.* 1958, i, suppl., p. 170.
7. Moncrieff, A. A., Soddy, K. Circular letter from British Pædiatric Association and National Association for Mental Health, July 29, 1948.
8. *Lancet*, March 7, 1959, p. 481.
9. Observations on the draft circulars of the Ministry of Health and Ministry of Education on child guidance.
10. Child Guidance and Speech Therapy. H.M. Stationery Office, 1958.

would not impair the essential cooperation with the educational services. The educational psychologist would continue to work in the schools part-time, as is wisely recommended in the Ministry of Education's circular. As the Ministry says, " child guidance " in its broadest sense is synonymous with education, but this is a poor reason to base therapeutic services on schools: the main work of the clinic is to examine and treat sick children; and it always will be, however much its staff engages in prophylaxis.

The Ministry of Health,[11] which has endorsed this circular, must be relieved that the proposals call for no great expansion in the N.H.S. budget. But the present policy represents no saving to the nation; and administrative convenience should not be allowed to delay desirable changes. Perhaps the two Ministries will have to think again. They agree on the need for recruiting staff of high quality; but they will make little headway unless they create conditions in which the staff can work happily and with satisfaction.

" Ascending " Pyelonephritis

ATTENTION has repeatedly been drawn to pyelonephritis arising unexpectedly where the kidney is primarily involved.[12–14] Renal infection accompanied or preceded by an infected lesion (often obstructive) in the lower urinary tract [13] is probably much commoner; and this type of infection (termed " ascending " infection or " surgical kidney ") is often accepted philosophically as almost inevitable. Evidence (often purely experimental) has been brought forward of four different routes by which infection from the bladder may reach the kidney—by blood spread, by the lymphatics, by the ureteral lumen, and by the ureteral wall—but there is no consensus of opinion as to which, if any, of these is the commonest. Thus prophylactic treatment is directed at no focal point, and it is often unsuccessful.

TALBOT [15] suggests that functionally the lower part of the ureter works not only in the peristaltic waves of the whole ureter but also with the bladder wall as a ureterovesical valve, the outer muscle layer merging with that of the bladder and having identical parasympathetic ganglia. First in patients with spinal-cord injury and thereafter in patients with mechanical obstruction, TALBOT showed radiographically that the dilatation of the ureter with reflux of urine started at the lower end and advanced upwards only gradually: he reasons that this dilatation and reverse peristalsis are due, not to obstruction, but to paralysis of the ureteric wall as the result of infection, and that the infection spreads up the ureter, not in the lumen, but primarily in the structures of its wall, thence involving the interstitial tissues in the kidney. While pyelonephritis may be hæmatogenous in origin, especially if the primary focus is not in the urinary tract, he concludes that, when it follows infection in the bladder, ascent via the subepithelial tissues of the bladder, ureter, and kidney pelvis is more probable. It is almost impossible, however, to establish histologically, at a much later date and from evidence of chronic infection and fibrosis, the initial order of the infection, or even to ascertain that the infection has spread up the subepithelial tissues and not entered from the lumen. TALBOT does not believe that infection is spread by the lymphatics, except as a secondary feature, since the major lymphatic drainage of the bladder is into the pelvic and iliac chains. He points out that WINSBURY-WHITE's beautiful demonstration [16] in animals of the spread of indian-ink and of dead and living tubercle bacilli from the lower genital and urinary passages via the periureteral lymphatic channels to the interstitial tissues of the kidney is not proof that pyogenic organisms follow the same route in man. Ascent of infection via the lumen is manifestly also possible, though not necessarily primary; TALBOT has shown reflux of radio-opaque material, and in acute cases ALLEN [17] describes the ureter as continuously infected from the site of obstruction up to the kidney.

On the other hand, GORRILL [18] supports the hæmatogenous school. He states that in catheter fever the cause is bacteriæmia due presumably to bacteria being squeezed into the lymphatics and blood-stream by the passage of the instrument. He points out that the one good example of ascending infection is pyelonephritis in children, where the 3:1 preponderance in females is most easily explained by soiling of the perineum and shortness of the urethra, which favour infection of the bladder and thence, by direct reflux or possibly by hæmatogenous spread, the kidneys. GORRILL [19] and others have already shown experimentally that obstruction of a ureter will lead to infection of the kidneys from the blood-stream—though healthy kidneys are infected only by a few organisms, such as *Staphylococcus aureus*.[20] Necropsies have confirmed blood spread from infections of the lower urinary tract: in male infants with urethral obstruction who have died in three weeks from coliform meningitis the dilated bladder was infected but the dilated ureters and pelves were not infected; adults with cystitis die from lung abscesses without infection of the kidneys; and adults with urinary obstruction and cystitis die from pyelonephritis without any detectable infection of the ureters.

As GORRILL [18] points out, the route of infection is not purely an academic question: if ascending infection is the chief cause, then it should be possible greatly to reduce the incidence; but if bacteria are regularly shed into the blood (for instance, from bowel or bladder) and thus reach a kidney susceptible to hæmatogenous infection owing to obstruction in the urinary tract, the problem is quite different. At present, it must be admitted that the infection may spread either by ascent of the ureter or by the blood-stream, and there is no way of discovering in any individual case which route may be followed. Treatment therefore should consist, not only in systemic administration of antibiotics to which the

11. Circular 3/59, H.M.(59)23; March 10, 1959.
12. Kass, E. H., Finland, M. *Trans. Ass. Amer. Physns*, 1956, **69**, 56.
13. Brod, J. *Lancet*, 1956, i, 973.
14. *Lancet*, 1956, i, 1000; *ibid.* 1956, ii, 1036.
15. Talbot, H. S. *J. Amer. med. Ass.* 1958, **168**, 1595.
16. Winsbury-White, H. P. *Brit. J. Urol.* 1933, **5**, 249.
17. Allen, A. C. The Kidney: Medical and Surgical Diseases; p. 342. London, 1951.
18. Gorrill, R. H. *Guy's Hosp. Rep.* 1958, **107**, 405.
19. Gorrill, R. H. *J. Path. Bact.* 1956, **72**, 59.
20. De Navasquez, S. *ibid.* 1950, **62**, 429.

infecting organism is susceptible, but also in relieving any obstruction by catheterising the bladder and (if no relief has been secured in forty-eight hours) the renal pelvis, in order to protect the parenchyma from the effects of stasis.[15]

The Professorial Unit

THE first professorial clinical units were established nearly forty years ago, and new ones are still being formed. Their original structure, which has proved very viable, survives virtually unmodified. Perhaps this is why the topic is seldom formally discussed; but the views of the powers and duties of clinical professors sometimes expressed in schools without clinical units suggests that misunderstanding of a unit's true function is still fairly widespread.

Prof. M. L. ROSENHEIM, in a presidential address to the Section of Experimental Medicine of the Royal Society of Medicine on March 10, reviewed the aims and working of a medical unit. A unit had to provide for the care of patients as completely and as well as other firms; it had special teaching commitments; and it had to pursue research and to train young doctors in research methods. It might be added that it is not the unit's job to act as a holding depot for M.R.C.P. candidates or time-expired registrars.

Units were established for the explicit purpose of introducing a university approach into clinical teaching, and the need for this is certainly no less than it was. Their special contribution does not lie in the organisation of teaching or the arrangement of systematic courses, although professors may well undertake these tasks. It lies rather in the attitude to knowledge of those actively engaged in research. Most clinical teaching still quite rightly deals with the practice of medicine as a craft, to be learnt by emulating its masters. This approach is rather surprisingly successful, as the efficiency of most house-officers testifies. The trouble is that medicine now develops so rapidly that what a student knows on qualifying will in the long run be less important than his ability to deal adequately with the flood of new information and ideas to which he will be exposed. It is this ability that teaching by research-workers may be expected to develop—by creating the habit of appealing to evidence rather than to authority. This is the very essence of the clinical unit's contribution to education; and isolation of the research-workers from the bulk of undergraduates in a department of experimental medicine is its antithesis.

A special research department, freed from teaching or routine clinical duties, may have advantages for some aspects of research. But the advantage is not all on one side: there are times when the availability of general clinical material and of wide clinical experience is of crucial importance. The truth is that clinical research is sufficiently various to justify different types of organisation, of which the professorial clinical unit in an undergraduate school is one of proved value.

Inquiries by Prof. W. S. PEART [1] indicate that about half the staff of a medical unit eventually leave to take consultant posts. In so far as this means that the scientific outlook is widely diffused throughout the health service it is to the good; but, as very few posts provide opportunities for research, it represents a loss of research potential that British medicine can ill afford. The administrative machinery for providing research sessions under the health service is now there, but until it is employed the full benefits of the research training given in clinical units cannot be realised.

1. *Lancet*, 1958, ii, 1232.

Annotations

THE RIGHT KIND OF CONTROL

ARE tranquillisers any good? In the five years since the introduction of reserpine and chlorpromazine there has been a spate of new products in this group, many of them minor variations of chlorpromazine.[1] Some of them have been submitted to controlled trials; but it would be a brave man who undertook to set down the indications for each. Meanwhile many doctors forsake the older products as each new one appears, and some prescribe mixtures of two tranquillisers and a sedative at once.

Controlled trials work satisfactorily in studies of, for example, the treatment of bacterial infections, where purely objective criteria are well established. But the techniques of controlled trials cannot be applied without fresh thought to many other problems, such as the relief of pain, the control of parkinsonism, and the treatment of schizophrenia. The designing of a trial does not depend on having a good statistician, but on thinking out beforehand the questions to be answered, and how these are to be answered truly.[2] Few so-called controlled trials, particularly of tranquillisers, reflect much realisation of this.

Kennedy [3] has analysed some important factors. Few people seem to be aware of the classical work by Beecher [4] and his colleagues on the relief of severe postoperative pain. While 75% of cases were relieved by 15 mg. morphine, over 30% were relieved by a placebo: in other words the patient's expectation had a powerful influence on the response. These workers showed [5] that there was a definite group of placebo-reactors among patients, and that pharmacologically inert placebos can give rise to such toxic effects as nausea, headache, dry mouth, drowsiness, and difficulty in concentrating—which often are reported as the side-effects of new drugs. Kennedy points out that, even in a double or triple blind clinical trial, the nursing and domestic staff and the patients have expectations (though the physicians may not), and this must modify the results. All too often these expectations are nourished by some evident side-effect of the drug under trial, in contrast with the absence of physical response to a bland placebo such as lactose. At Birmingham Mayer-Gross et al.[6] gave nicotinic-acid capsules to half of a group of 28 schizophrenic men and lactose capsules to the remainder, and asked the nurses to report the incidence of flushing. It was not until the fourth week of observation

1. Laurence, D. R., Pond, D. A. *Brit. med. J.* 1958, i, 700. Rodger, T. F., Mowbray, R. M., Roy, J. R. Topics in Psychiatry. London, 1958.
2. See *Lancet*, Jan. 31, 1959, p. 243.
3. Kennedy, A. *Pharm. J.* 1959, **182**, 5, 23.
4. Beecher, H. K. *J. Amer. med. Ass.* 1955, **158**, 399.
5. Lasagna, L., Masteller, F., von Feisinger, J. M., Beecher, H. K. *Amer. J. Med.* 1954, **16**, 770.
6. Mayer-Gross, W., Harris, A. D., Letemendia, F. Proceedings of the First International Congress of Neuro-psycho-pharmacology, Rome (in the press).

that something like a maximum of flushes in the treated group was recorded (9 out of 14), and simultaneously flushing began to be reported also in an increasing number of the control group. Unfortunately since the urines were not tested for the drug we cannot be sure that all the treated patients took their capsules, or at least the right ones; but it seems likely that the nurses' expectations were also a factor in this result. Testing urine for signs of a drug supposedly taken [7] is, incidentally, rarely used in clinical trials; yet ward experience has shown that some patients secretly reject their tablets, and Neve [8] found that one in ten of his were avoiding their chlorpromazine. The patient's personality is important: the suspicious, the suggestible, the hypochondriac, the anxious [9] may respond differently in the trial situation and distort the result, especially if control and treatment groups are not matched for such factors. Mayer-Gross et al. matched their groups for age and sex, length of hospital stay, and severity of illness, and then found that the two groups differed significantly in weight and systolic blood-pressure, both of which might influence a drug response. More such tests of trial methods are needed.[10]

Kennedy points out that assessment of a response by means of a rating scale carries two risks—first, that steps on the scale are not quantitatively equivalent, so that a score of 4 is not twice 2; and, secondly, that observers cannot hold a steady baseline from day to day. Some observers are by personality quite as unsuited for such trials as are some of the patients they propose to study; others become better observers after training. Even so, the coordination of several observers on a common scale involves severe problems. Where nurses are to be used to make frequent observations, even of something simple such as temperature, in addition to their usual ward duties, it is essential to make sure that the special duties can be fitted into the ward routine, and that they have enough time. It is also important to warm the observation team with enthusiasm, and provide some independent checks on their observations. The commonest error in testing new remedies is to forget that both patient and nurse are human.

A good many of these difficulties shrink if the preliminary thinking is straight. Instead of submitting whole wards of patients indiscriminately to a drug, when the few responding are swamped by the resistant battalions, precise diagnostic categories should be selected. Instead of a "kill-or-cure" trial, in which patients are rated overall as improved or not improved, precise questions of detail should be set. Thus in a recent inquiry [11] the trial was restricted to manic patients and to a single question—Does reserpine shorten manic attacks? The question whether reserpine also prevents recurrences is separate. Some drugs probably neither prevent recurrences nor shorten the attack but modify symptoms—reducing hypermotility without affecting flight of ideas, for instance. Trials at Leeds [12] suggest that, while benactyzine has little effect on the anxiety of anxiety neurotics, it does modify the somatic expression of the neurosis. This contribution to clinical pharmacology may help the chemist to synthesise compounds of greater practical use. A trial which does not merely result in a "yes" or a "no" but also provides new leads is greatly to be preferred, and the significance of possible outcomes should be considered before the trial is begun. Nor should it be forgotten that clinical experience and clinical observation, today rather undervalued, are essential.

7. See *Lancet*, 1958, i, 418.
8. Neve, H. K. *J. ment. Sci.* 1958, **104**, 488.
9. Roberts, J. M., Hamilton, M. *ibid.* p. 1052.
10. Glaser, E. M., Whittow, G. C. *Clin. Sci.* 1954, **13**, 199.
11. Watt, D. C. *J. Neurol. Neurosurg. Psychiat.* 1958, **21**, 297.
12. Hamilton, M. *J. ment. Sci.* 1958, **104**, 1062.

ACUTE RESPIRATORY FAILURE

PULMONARY disease always interferes to some extent with alveolar ventilation; when more than a certain number of alveoli are underventilated, carbon dioxide is retained in the blood, which is incompletely oxygenated. This condition can be rectified only by an increase in alveolar ventilation, which may be achieved either spontaneously or by pharmacological or mechanical means. Disease may also increase the mechanical barrier separating blood and alveolar gas by accumulation of exudate around the alveoli. This has no effect on the passage through the alveolar wall of carbon dioxide, which dissolves freely in the exudate; in this respect the exudate may be regarded as an extension of the blood-plasma. But the same is not true of oxygen, which is twenty-five times less soluble than carbon dioxide. Thus the result of exudation around the alveolus is arterial suboxygenation without retention of carbon dioxide. Emphysema is typical of diseases associated with alveolar hypoventilation, and lobar pneumonia of diseases in which the mechanical barrier is increased with consequent suboxygenation. The lesions bringing about these two types of disturbance often exist side by side in the same lung. These points are well illustrated in articles on earlier pages of this issue by Dr. Herzog and his colleagues and by Dr. Davidson.

Both these articles underline the importance in acute respiratory disorders of restoring normal oxygenation. Dr. Davidson rightly suggests that in dealing with acute episodes in severely emphysematous patients the attendant risk of increasing retention of carbon dioxide during administration of oxygen is quite justifiable, even if coma supervenes: this complication can often be averted by administration of powerful respiratory stimulants such as niketha mide and bemegride or, more certainly, by employing mechanical respirators. For oxygen therapy to be effective a clear airway is essential; and Dr. Davidson points to the usefulness of tracheostomy, which facilitates evacuation of pus and mucus from the bronchial tree as well as improving alveolar ventilation and providing a means of initiating mechanical respiration.

It is vitally important to recognise respiratory obstruction. This is marked by powerful contraction of the muscles of respiration, especially of the accessory muscles, with indrawing of the intercostal spaces during inspiration, often combined with absent breath-sounds and accumulation of exudate in the larger airways. When the airway is obstructed nearly all the patient's energy is canalised into breathing; and any relief of this load may tilt the balance in his favour. One of the main advantages of mechanically assisted respiration is that it diminishes the demand of the respiratory muscles for oxygen, more of which thus becomes available to other tissues. In the final stages of oxygen deprivation respiratory efforts may cease suddenly, though usually there is a premonitory period of irregular violent inspiratory effort alternating with phases of absolute muscular relaxation. Respiratory stimulants should be used cautiously. They are primarily indicated in cases of central respiratory depression due to narcotics (including endogenous carbon dioxide). It is manifestly useless to administer them when the airways are obstructed, since anoxia is already stimulating powerful motor discharge from the respiratory centre, and they

can only give rise to undesirable waste of energy by further stimulating the already ineffective contractions of the respiratory muscles.

ANÆMIA AND ALIMENTARY DISORDERS

THE non-specific treatment of any anæmia with a battery of hæmatinics cannot be too strongly condemned. Even those without a special interest in blood diseases now appreciate that iron-deficiency anæmia almost invariably responds to iron in some form, and that liver extracts, cyanocobalamin (vitamin B_{12}), and folic acid should be reserved for the various types of megaloblastic anæmia. For this reason last week's report by Dr. Michaelides and Dr. Philis [1] on the value of intrinsic factor in the management of a case of hypochromic anæmia may seem provocative. They describe a patient with severe hypochromic anæmia, associated with a rolling type of hiatus hernia, in which ferric iron was not absorbed unless a reducing substance was given with it. Cyanocobalamin, normal gastric juice, and a commercial preparation of Castle's intrinsic factor were all effective. This observation led them to conclude that an intrinsic reducing agent present in normal gastric juice is necessary for the assimilation of iron, and they suggest that this reducing agent may be identical with Castle's intrinsic factor.

This hypothesis, and the experimental evidence on which it rests, leaves many questions unanswered; but it underlines some of the difficulties which continually recur in the interpretation and management of deficiency states. Many substances which used to be considered essential only to particular organs have been found to be needed by most tissues. Cyanocobalamin and iron, for example, are necessary not only for blood formation but for the normal metabolism of most, if not all, cells in the body. The lining of the gastrointestinal tract and the bone-marrow are especially sensitive to shortage of these only because of their extremely rapid cellular turnover. The initial clinical manifestations of a deficiency state are usually mild; and later, when obvious organic lesions have developed, it becomes difficult to distinguish cause from effect. For many years it was believed that achlorhydria—now recognised as a manifestation of iron deficiency—predisposed to inefficient absorption of iron. Far from being responsible for the iron deficiency it is now recognised as one of its results. Many patients with achlorhydria can still absorb iron from their food, and the addition of hydrochloric acid is of no special benefit to them.[2] Probably the low serum-iron causes the gastric mucosal changes which lead to achlorhydria.

Other gastrointestinal lesions, however, are by no means blameless in the development of secondary iron deficiency. Partial gastrectomy is so common an operation that the hypochromic anæmia which often follows it has become a common disease. Chronic blood-loss can rarely be incriminated as its cause, nor is iron intake necessarily inadequate. By giving a normal bulk of food containing radioactive iron, it has been shown that iron absorption from food is diminished, whereas organic and inorganic iron given on an empty stomach are still readily absorbed.[3–5] Witts [6] has suggested that the diminished absorption may be due to the impaired function of the stomach as a " hopper " for holding the food while iron is converted into a form in which it can be absorbed. Callender,[7] on the other hand, points out " that there may be other local secretory factors as yet undefined which may influence the absorption of iron ".

The anæmia of patients with hiatus hernia is nearly always of a hypochromic microcytic type (there have only been occasional reports of macrocytic anæmia) [8]; and usually the anæmia is ascribed to chronic blood-loss from œsophagitis or ulceration, aggravated by starvation. It is unlikely, however, that this is the whole explanation, for many patients with anæmia have no ulceration. (Blood-loss may be more important in children, in whom hiatus hernia is especially prone to be complicated by anæmia.) The alternative suggestion by Michaelides and Philis—that iron is not absorbed because of lack of intrinsic factor—should be considered, even though it does not account for a patient's negative response to previous intensive courses of parenteral iron. This is hard to reconcile with the response to oral iron after administration of intrinsic factor. Alimentary-tract anæmias not infrequently show the features of both iron deficiency and megaloblastic change—for instance, after total or subtotal gastrectomy and in steatorrhœa—and it seems possible that the case described by Michaelides and Philis was not entirely straightforward. This work will have done valuable service if it leads to further investigation of the relation and interdependence of the various substances necessary for normal hæmopoiesis; but it does not invalidate orthodox teaching on their specific indications in treatment.

GENERAL-PRACTITIONER MATERNITY BEDS

IN many parts of the country family doctors and consultants are having difficulty in arranging for maternity patients to be admitted to hospital, even when there are sound medical or social reasons against a domiciliary confinement. Thus at some London antenatal clinics the patient is advised to call in her family doctor when labour starts and ask him to arrange admission through the Emergency Bed Service.[9] In the *Manchester Guardian* last month [10] a consultant complained that he had been unable to book a bed for a patient who expected her first baby at the end of September. These incidents are particular expressions of the Cranbrook Committee's general recommendation that, taking the country as a whole, beds should be available for 70% rather than 64% of all deliveries.[11] As is so often the way, difficulties created by shortage are aggravated by maldistribution. Beds are available for 90% of confinements in West Ham, but in Middlesbrough there are beds for only 33%.

The number of beds is only one of the variables in the problem; bad housing can sharply increase the proportion of mothers for whom a domiciliary confinement can be an uncomfortable if not hazardous experience. In Manchester, for instance, an inquiry made last year for the Minister of Housing and Local Government showed that out of 200,000 dwelling-houses 60,000 are unfit. A large proportion of these are working-class houses, and in some districts the need for extra maternity beds is consequently acute. As a result, the health committee of the city has

1. Michaelides, G. J., Philis, H. Chr. *Lancet*, March 14, 1959, p. 552.
2. Moore, C. V., Dubach, R., Minnich, V., Roberts, H. K. *J. clin. Invest.* 1944, **23**, 755.
3. Smith, M. D., Mallet, B. J. *Clin. Sci.* 1957. **16**, 23.
4. Chodos, R. B., Ross, J. F., Apt, L., Pollycove, M., Halkett, J. A. E. *J. clin. Invest.* 1957. **26**, 314.
5. Pirzio-Biroli, G. Bothwell, T. M., Finch, C. A. *J. Lab. clin. Med.* 1958. **51**, 37.
6. Witts, L. J. *Lancet*, 1958, ii, 259.
7. Callender, S. T. *Brit. med. Bull.* 1959, **15**, 7.
8. Murphy, W. P. *Bull. New Engl. med. Center*, 1942, **4**, 7.
9. King Edward's Hospital Fund for London: annual report 1957; p. 24.
10. *Manchester Guardian*, Feb. 24, 1959, p. 6.
11. See *Lancet*, Feb. 21, 1959, p. 397.

for some time been considering another of the Cranbrook Committee's recommendations—the provision of beds for general-practitioner obstetricians. A deputation from Manchester, consisting of members of the regional hospital board, the corporation, the board of governors, and the executive council, have asked if they may meet the Minister of Health to discuss the idea of opening maternity homes in some congested districts. Dr. C. Metcalfe Brown, the medical officer of health, has suggested that the homes should have 20-25 beds and be staffed by general practitioners and municipal midwives (though not necessarily exclusively so). It has not yet been decided whether the homes should be set up by the regional hospital board or by the local health authority. There would apparently be no legal hindrance to the board's providing homes of this kind; but, if the board did not feel able to accept this new responsibility, the local authority would consider doing so. As the homes would in fact be offering the equivalent of domiciliary care, near, instead of inside the patients' own homes, Dr. Metcalfe Brown believes that the general practitioner could call on consultant advice exactly as he does now, asking, should need arise, for the transfer of his patient to hospital or for a domiciliary visit (to the nursing-home) from a consultant.

TORULOSIS OF THE NERVOUS SYSTEM

FUNGUS infections of the central nervous system are rare; but Rose et al.[1] have described three such cases, all of which were fatal. Similar cases have been reported only occasionally in the United Kingdom; but we have heard of two in a general hospital in four years, and possibly the diagnosis is sometimes overlooked. The first verified case was described by Busse [2] in 1894, and the first cases in this country in 1930 [3] and 1938 [4]; but considerably more cases have been reported in the United States and Australia. The organism, variously known as *Torula histolytica* or *Cryptococcus neoformans*, is widely distributed and is found in the mouths of healthy people, only rarely causing disease. The common sites of infection are the lungs and the central nervous system.

Neurological involvement is of two main types: subacute meningoencephalitis with lymphocytic response in the cerebrospinal fluid, which is the commoner form; and intracranial toruloma, giving the clinical picture of an intracranial tumour. In the meningeal form the disease usually develops over the course of several weeks; especially if there is also a pulmonary lesion, it may superficially resemble tuberculous meningitis, but there are often only slight pyrexia and very slight changes in the erythrocyte-sedimentation rate and white blood-cell count. Intracranial toruloma may be accompanied by torula meningitis or may arise without signs of meningeal irritation and with a normal cerebrospinal fluid. In the cases of meningitis the diagnosis is made by finding the organisms in the cerebrospinal fluid, and these are most readily detected in wet films of the centrifuged deposit stained with nigrosin or indian-ink. If this examination is not carried out, the organisms may be confused with lymphocytes. Cultures should be made on Sabouraud's medium, but growth may develop only after several days. Unfortunately in some cases the organism cannot be found, and in one of Rose's patients it could be neither cultured nor found despite repeated attempts.

Until recently treatment has been ineffective. On a few occasions an intracranial toruloma has been removed surgically, but there has been a grave danger of fatal torula meningitis ensuing. Krainer et al.[5] reported the removal of a toruloma under the left frontal lobe, and the patient remained well eleven months afterwards. In 1951 Wilson and Duryea [6] reported the successful use of an antifungal antibiotic, 'Actidione' (cycloheximide), in a patient who subsequently was free of symptoms and had sterile cerebrospinal-fluid cultures twenty months after the diagnosis had been made. But Boshes et al.[7] treated three patients with this substance without success, and in one case there was an acute exacerbation a few days after treatment was started. More promising results have recently been reported with the use of amphotericin B[8]; of ten cases of torula meningitis treated in this way by Rubin and Furculow [9] eight were alive two to fourteen months later, and in seven of these the cerebrospinal fluid was consistently sterile.

1. Rose, F. C., Grant, H. C., Jeanes, A. L. *Brain*, 1958, **81**, 542.
2. Busse, O. *Zbl. Bakt.* 1894, **16**, 175.
3. Smith, F. B., Crawford, J. S. *J. Path. Bact.* 1930, **33**, 291.
4. Greenfield, J. G., Martin, J. P., Moore, M. T. *Lancet*, 1938, ii, 1154.
5. Krainer, L., Small, J. M., Hewlitt, A. B., Deness, T. *J. Neurol. Neurosurg. Psychiat.* 1946, **9**, 158.
6. Wilson, H. M., Duryea, A. W. *Arch. Neurol. Psychiat.* 1951, **66**, 470.
7. Boshes, L. D., Sherman, I. C., Hesser, C. J., Milzer, A., Maclean, H. *ibid.* 1956, **75**, 175.
8. Appelbaum, E., Shrokalkos. *Ann. intern. Med.* 1957, **47**, 346.
9. Rubin, A., Furculow, M. L. *Neurology*, 1958, **8**, 590.

OVERSEAS VISITS BY STUDENTS

THE appeal by Mr. Moore and others for the British Medical Students' Trust (p. 636) deserves to succeed. The Trust, which owes its origin to the British Medical Students' Association, aims to provide travel grants for students proposing to study at universities and hospitals abroad, and to defray the expenses of delegates of the B.M.S.A. attending meetings of the International Federation of Medical Student Associations. The Trust is a development of the B.M.S.A.'s Student Travel Fund, founded in 1954, and its International Delegates' Fund. From the two funds altogether £1893 has been distributed (S.T.F. £505, I.D.F. £1388), and a very large proportion of this total was subscribed by students themselves. Under the Trust the expenditure on delegations is expected to remain about the same, but it is hoped to enhance greatly the amount spent on travel.

The potential value of visits by medical students to overseas centres is clear. For a student confined to the, often narrow, circle of his own medical school it is difficult to picture other methods of teaching, other settings for medical practice, and different—perhaps better, perhaps worse—resources for practice. Hitherto it has been unusual for men and women in medicine to gain grants for overseas visits until they have qualified and are perhaps on the way to establishing themselves. And yet it is in undergraduate days, before habits of thought and plans for the future have solidified, that the impact of a different medical scene is likely to be greatest. Nor will the value of travel grants be confined to those who go abroad; for on their return those who have been abroad will fertilise the minds of contemporaries who have stayed here. For this reason the new Trust should have the support of medical educationists and others.

THE INDEX and title-page to Vol. II, 1958, which was completed with THE LANCET of Dec. 27, is published with our present issue. A copy will be sent gratis to subscribers on receipt of a postcard addressed to the Manager of THE LANCET, 7, Adam Street, Adelphi, W.C.2. Subscribers who have not already indicated their desire to receive indexes regularly as published should do so now.

Special Articles

RAPID METHODS FOR ESTIMATING SOME SERUM-PROTEINS AND THE SIGNIFICANCE OF ABNORMAL RESULTS

GEORGE DISCOMBE
M.D., B.Sc. Lond.
PATHOLOGIST, CENTRAL MIDDLESEX HOSPITAL, LONDON, N.W.10

NOWADAYS every patient has the right to expect proper investigation of any illness. This proper investigation should be done as cheaply and simply as possible—a requirement that is reinforced by the fact that time and labour given to some recondite test for the benefit of one patient may deprive more than one other patient of benefits from some simple tests. Methods of investigation should constantly be under critical review in the hope that the same, equivalent, or more useful information can be obtained with less labour.

The estimation of serum (plasma) proteins is becoming more popular, and in most laboratories this is done quantitatively by a salting-out procedure or by filter-paper electrophoresis. These methods are laborious, and I therefore decided to review the amount of clinically useful information obtained by each technique.

At present plasma-proteins are classified, in terms of electrophoretic analysis, as albumin and α_1, α_2, β, and γ globulin. There is nothing sacrosanct in this classification, and each of these components is multiple: for example, the α_2-globulin fraction contains several enzymes, glycoprotein, and lipoprotein; the β-globulin can be separated into two components, and contains lipoprotein as well as siderophilin and some antibodies; while the γ-globulin can be shown to contain at least three major components and most of the ordinary antibodies. For some purposes, no doubt, this classification will be made finer, as by Grabar's immuno-electrophoretic technique; and for others quite different classifications may be invoked—for example, cryoglobulins and macroglobulins, depending on temperature change and sedimentation respectively. It is quite clear that, although the values of "globulin" and "albumin" obtained by salting-out procedures may be persuaded to approximate to the values deduced from electrophoresis, the two components thus defined are never electrophoretically pure and apparent agreement is secured by neutralisation of errors.

In disease the largest and clinically most important changes appear in albumin and γ-globulin—so much so that, except in nephrosis, increases in "globulin" found by salting-out are due to variations in γ-globulin. Changes in α and β globulins may be relatively large, but are absolutely small—again excepting nephrosis. In rare cases of myelomatosis the paraproteins may migrate in the position of α_2 or β globulins, though more commonly between β and γ or in the region of the γ-globulins, and they are usually electrophoretically homogeneous. It seemed, therefore, that if true albumin and true γ-globulin could be directly estimated, these measurements, together with that of total protein and in a few cases of fibrinogen, would provide as much (or more) useful information as could the traditional methods, and often as much as would be obtained by electrophoresis. Even some measure of the $\alpha+\beta$ globulins could be obtained, though, since this would be by difference, the estimate would needs be inaccurate and only gross changes such as those of nephrosis or of α or β myeloma would be indicated. Consistency between workers is at least as important as accuracy, and a tolerance of $\pm 3\%$—about that for calibrated glassware—should be considered reasonable.

Methods

Total Protein

Abdel-Wahab et al. (1956) tried several methods for estimating total protein and finally chose the specific-gravity method of Phillips et al. (1945) as the most consistent and of reasonable accuracy, thus agreeing with Waldenström (1949). This method is based on the study of drops falling or rising in copper-sulphate solutions of different specific gravity, and the specific-gravity interval between the solutions is usually 0·001—equivalent to 0·36 g. protein per ml. Since specific gravity can safely be estimated to 0·001, or even to 0·0005, the accuracy of $\pm 0{\cdot}18$ g. per 100 ml. or better is of the desired order. This method is extremely satisfactory; sera frozen for several years have been found, when thawed, to give results identical with those obtained when fresh.

Albumin

Albumin has hitherto been estimated by salting-out or by electrophoresis. New methods based on the protein error of indicators have been introduced by Bennhold et al. (1951), by Bracken and Klotz (1953), and by Rutstein et al. (1954). Bennhold's method is complex; of the less complex procedures using the indicators methyl-orange (Bracken and Klotz 1953) and those formed by coupling diazotised anthranilic acid with phenol (Rutstein et al. 1954), guiaicol, β-naphthol, and 2-naphthol-3 : 6-disulphonic acid (R-acid) (G. Discombe, unpublished), the methyl-orange as used by Bracken and Klotz gave the largest change in colour and was therefore adopted. It was subsequently found that the change in extinction at 550 mμ (Ilford 605 filter) was proportional to the logarithm of the protein added, so that the calibration curve is linear on semilogarithmic paper. Calibration is with bovine or human albumin, and γ-globulin does not interfere. Electrophoretically pure undenatured α and β globulins have not been available, but studies with sera containing excess of these components show that they do not alter the results appreciably, though in the severest cases of the nephrotic syndrome the albumin level determined by the indicator method is always higher than that deduced from electrophoresis; even so, it is always grossly subnormal so that no clinical difficulty will occur. Hæmolysis, turbidity, and intense jaundice produce erroneously low results; and occasionally, for no apparent reason, the reagent suddenly becomes unsatisfactory, the optical density becoming smaller and the slope increasing; it is therefore necessary to check the optical density and to determine a point on the calibration curve daily. For satisfactory results, $E_{1\,cm.}^{605}$ should exceed 0·67 for the pure reagent.

Gamma-globulin

Gamma-globulin can be determined by ammonium-sulphate precipitation (de la Huerga and Popper 1950, Levin et al. 1950) or by the zinc-sulphate turbidity method of Kunkel (1947). Discombe et al. (1954) found that Kunkel's method was simple and reliable provided that changes in pH are avoided by keeping the reagent in a vessel to which carbon dioxide cannot gain access and by adding the serum to reagent with a pipette manipulated by a teat or similar device. They estimated the correlation coefficient between turbidity and electrophoretically determined γ-globulin to be $+0{\cdot}91$; the equation relating the two is less satisfactorily determined, for, though different observers estimate the slope to be within the range 0·05–0·065 (a fairly narrow range), the concentration of γ-globulin corresponding to zero turbidity ranges from 0·5 to 1·5 g. per 100 ml. These discordant figures probably result from the interference of the filter-paper which supports the dyed protein; elution methods, or photometry of transparent cellulose-acetate membranes, will probably lead to more consistent results; but for the time being the levels of γ-globulin deduced from zinc-turbidity tests are best recorded in arbitrary units, and no attempt to convert them into concentrations should be made.

Fibrinogen

Fibrinogen can be rapidly determined by the method of Stirland (1956) with an accuracy of about ±5%. Its level correlates highly with the erythrocyte-sedimentation rate (E.S.R.) ($r = +0{\cdot}71$ [Westergren and Stavenow 1951]); so its determination will rarely be needed except in suspected hypofibrinogenæmia, or when it is thought that a high E.S.R. may be due to a myeloma paraprotein.

TECHNIQUES IN DETAIL

These very simple procedures are performed thus:

Albumin.—Store the reagent in a bottle which feeds a 5 ml. automatic pipette. To a 5 ml. portion add 0·2 ml. serum, determine extinction in a 1 cm. cell with filter 605 and refer to a calibration curve made with 6, 5, 4, 3, 2, and 1% solutions of electrophoretically pure human or bovine albumin. Check with one of these standards daily.

γ-Globulin.—The zinc-sulphate reagent is kept in a 'Derona' type burette or pipette protected from access of atmospheric carbon dioxide by a soda-lime guard tube. Place 6 ml. reagent in a test-tube, add 0·1 ml. serum with a teat pipette. Stand 30 minutes, determine extinction in a 1 cm. cell with filter 608, and express in terms of Kunkel's barium-sulphate units.

Fibrinogen.—Place 3 ml. 1% sodium chloride in each of two test-tubes and add 0·2 ml. plasma to each. Place one in the 56°C water-bath for 15 minutes, cool, and determine extinction with the 608 filter or at 660 mμ using the unheated tube as blank. Express as Kunkel units, 1 Kunkel unit being equivalent to 42·8 mg. fibrinogen per 100 ml. under these conditions. If turbidity exceeds 20 units, the calibration ceases to be linear, so the test should be repeated using less plasma. If larger volumes of liquid are needed, use 5 or 6 ml. sodium chloride and up to 0·5 ml. plasma, making the appropriate correction in the calculation.

A batch of 20–30 sera for total protein, albumin, γ-globulin, and thymol-turbidity tests can be dealt with by one technician in an afternoon.

Discussion

Although everybody wants to confirm a diagnosis by tests on a single sample of blood, Wang (1953) showed that, in the differential diagnosis of jaundice, conclusions drawn from analyses of a single sample were erroneous in 6–10% of cases and equivocal in 23%; and his experience will be repeated in other problems of differential diagnosis. Changes in serum-protein cannot be related to individual "diseases"; rather do these changes reflect changes in physiological state, so in interpreting them we must use our knowledge of the natural history of disease and of general chemical physiology to obtain a picture of the dynamic physiology of the patient.

Non-reactive Changes in the Serum-proteins

There are a few apparently inborn metabolic errors in which gross deviations from the normal pattern of protein distribution are found. Bennhold et al. (1954) recorded cases in which serum-albumin was completely absent, and Knedel (1957) others in which two electrophoretically distinguishable "albumins" were present; while Homburger and Petermann (1949) described a familial dysproteinæmia in which a reduction in the level of circulating albumin seemed important. Wilson's disease (hepatolenticular degeneration) is accompanied by a reduction in serum-amine-oxidase which could be detected among the α_2-globulins by appropriate reagents (Uriel 1958). Congenital agammaglobulinæmia (Bruton 1952, Firkin and Blackburn 1958) is accompanied by absence of plasma-cells from the body (Good and Zak 1956) and Gitlin et al. (1956) have shown that, in addition to the almost complete absence of γ-globulin, at least two components of β-globulin are absent in these cases; so we may conclude that plasma-cells produce not only γ-globulin but also some components of β-globulin.

Finally, one must recognise the hypercatabolic hypoproteinæmia of Schwartz and Thomsen (1957) in which the circulating albumin is halved and the half-life of an albumin molecule is only a third of that found in health.

Changes due to Neoplasia of Plasma-cells and Lymphocytes

Fagraeus (1948) showed conclusively that plasma-cells produced the ordinary antibodies. Patients with malignant plasmacytoma (myelomatosis) often have greatly increased globulin—usually in the form of an abnormally homogeneous γ-globulin, though β and α_2-globulin are not very rare and sometimes the globulin moves as a band between β and γ globulins (Wuhrmann and Wunderly 1957). Porges (1956) drew attention to the almost complete absence in these cases of the normal components of γ-globulin which should border the myeloma γ-globulin, and I have observed the complete absence of any component of γ-globulin in a case of α_2-myeloma. Kunkel et al. (1951) showed that myeloma γ-globulin, though related to normal γ-globulin, was not identical with it, and Larson and Tomlinson (1953) showed that patients with myelomatosis showed little response to antigenic stimuli, in this resembling patients with chronic lymphatic leukæmia. This observation explains such oddities as Bøe's (1945) case in which nine attacks of pneumonia preceded discovery of the underlying myelomatosis. It is useful to think of myeloma cells as not only morphologically but also physiologically dysplastic, producing a protein similar to, but not identical with, that produced by normal plasma-cells. Patients whose normal plasma-cells have been replaced by myeloma cells would be expected to produce no antibodies. That the cells can produce a "chemically dysplastic" molecule was shown by a personal case in which an electrophoretic γ-globulin failed completely to produce a precipitate with Kunkel's zinc reagent.

The relationship between myeloma and Waldenström's macroglobulinæmia has been obscure. In some laboratory animals antibodies are known to be formed, at least in part, by cells which are morphologically lymphocytes. Many patients with macroglobulinæmia have bone-marrow containing a gross excess of lymphoid cells (Bichel et al. 1950, Rörvick 1950), and it seems reasonable to suppose that the morphological correlate of macroglobulinæmia with high sedimentation (S19–20) is a lymphocytosis; whereas excess production of globulins of normal sedimentation (S7–10) is accompanied by plasmacytosis. A simpler but less precise formulation is that lymphocytes, if not too dysplastic, produce macroglobulins whereas plasma-cells produce globulins of normal size. Svartz's (1957) observation that in rheumatoid arthritis the factor responsible for the Rose-Waaler hæmagglutination test is a macro-γ-globulin of S19–20, and is cold-precipitable, while the lupus-erythematosus factor is a γ-globulin of normal size and is not cold precipitable, is easily explained on this basis.

Reactive Changes in Serum-protein

Changes in albumin are non-specific. An increase above normal is seen only in severe dehydration, and then in proportion to the increase in total plasma-protein. Reduction in albumin is quite common, occuring in almost every febrile illness after a few days; even in infectious mononucleosis Sterling (1949) found an albumin level below the lower limit of normal in each of the nine cases he studied; considerable reductions occur in almost all long-continued illness irrespective of the pathological process.

Reactive processes rarely depress the serum-albumin below 3 g. per 100 ml.; but gross malnutrition, whether

primary or secondary to hepatic cirrhosis, and the nephrotic syndrome are associated with figures often below 2·5 g. per 100 ml. and occasionally below 2 g. per 100 ml.; although in nephrosis the figure for albumin found by the methyl-orange method is always higher than that indicated by paper electrophoresis, it is always so low that no clinical error is likely.

Free-boundary electrophoretograms are obtained by measurements of refractive-index gradients, and therefore include with "protein" the considerable contribution to optical density of lipoids which travel chiefly with the α_2 and β globulins. Paper electrophoresis, in which the protein bands are stained, is not subject to this disadvantage, and agrees better with electrophoretograms made with ether-extracted serum, though few believe that quantification is much help and most prefer to depend on inspection of the electrophoretogram (Mackay et al. 1954). By paper electrophoresis, changes in β-globulin are found to be small, the large changes found in obstructive jaundice by free-boundary electrophoresis being due to β-lipoproteins: considerable increases are found in nephrosis, and in infective hepatitis β-globulin apparently plays a predominant part in bringing about the positive thymol-turbidity test (Albertsen and Heintzelmann 1950a, Albertsen et al. 1950, Dekemer 1951, Kunkel and Hoagland 1947). So far no specific test for β-globulins has been developed, though Bernfield et al. (1957) have developed a simple nephelometric method for the determination of β-lipoproteins.

The α-globulins, particularly the α_2 fraction, show larger and more important changes. These seem to be due to the increase in glycoprotein in pregnancy and during the acute or progressive phase of disease, whether infective, neoplastic, or traumatic (Keyser 1950, Shetlar et al. 1955, Stidworthy et al. 1957). This glycoprotein may be responsible for much of the early rise in E.S.R., for Shedlovsky and Scudder (1942) found that the correlation coefficient between E.S.R. and α-globulin was very high in fever, while Westergren and Stavenow (1951) found that in tuberculous patients the correlation between E.S.R. and the components of plasma-protein, estimated by free-boundary electrophoresis, was as seen in the accompanying table. This indicates quite clearly that, irrespective of the stage of the disease, patients with a raised E.S.R. tend to have high fibrinogen and low albumin levels, but that during the invasive period before treatment high E.S.R.s and high α-globulin are associated, whereas after treatment the α-globulin ceases to be related to the E.S.R. but the γ-globulin becomes associated therewith.

Jacox (1953) and Jacox and Gale (1951) developed a simple turbidimetric method for the estimation of total α-globulin, and this is now being studied in our laboratory. Shetlar et al. have shown that C-reactive protein is highly correlated with seromucoid (1955) and with serum-glycoprotein (1956) so that a rapid method of estimating either of these might prove useful. Possibly differentiation between α_2-glycoprotein and α_2-lipoprotein might be useful in differentiating the hyper-α_2-globulinæmia of nephrosis from that of cancer or infection, though this differentiation can usually be established clinically.

Increases in γ-globulin occur predominantly in diseases with a long course. Most infectious diseases show a small increase of 20–50% quite early (e.g., in glandular fever by the second week), but only in a few tropical infections (particularly leishmaniasis [Brahmachari 1917], trypanosomiasis, leprosy, and lymphopathia venereum) do really high γ-globulin levels of up to 6 g. per 100 ml. or more occur; the hyperglobulinæmia of schistosomiasis seems to be secondary to the hepatic cirrhosis (Faust and Meleney 1924). There is a type of endocarditis lenta rare in this country but apparently common in Spain in which bacteria cannot be found either in the blood or in the vegetations, but E.S.R. values are very high and γ-globulin levels are greatly increased (Permanyer-Macia and Cañadell-Vidal 1943, Trias de Bes et al. 1946, Jimenez-Diaz et al. 1949, Ball 1950); a corynebacterium has been isolated from marrow but not from blood (Jimenez-Diaz and Arjona 1949, 1950) and the globulin increase has been ascribed to the production of antibodies (Kürten 1929, Carballo and Lopez-Garcia 1946, Pagel 1949), though it seems as yet uncertain that the condition is not part of an autoimmune disease such as disseminated lupus erythematosus.

CORRELATION BETWEEN COMPONENTS OF PLASMA-PROTEIN AND E.S.R. (WESTERGREN AND STAVENOW 1951)

Component	Before treatment	After treatment	Before and after treatment
Fibrinogen ..	0·75 ± 0·05	0·53 ± 0·11	0·71 ± 0·05
Albumin ..	−0·74 ± 0·06	−0·54 ± 0·11	−0·76 ± 0·04
α-globulin ..	0·62 ± 0·05	0·14 ± 0·16	0·70 ± 0·05
β-globulin ..	0·18 ± 0·12	−0·15 ± 0·15	0·22 ± 0·09
γ-globulin ..	0·04 ± 0·12	0·39 ± 0·13	0·02 ± 0·05

Inconstant but often large increases are found in the acute phase of all the autoimmune diseases—notably disseminated lupus erythematosus, Hashimoto's disease, and most cases of exfoliative dermatitis. Smaller increases are found in rheumatoid arthritis, polyarteritis nodosa, and Wegener's granulomatosis; in these the rise may be detectable only in the later stages of the disease and after months of illness. Christenson and Dacie (1957) and Christenson et al. (1957) found that, where patients with acquired hæmolytic anæmia had cold autoantibodies of high titre in their serum, those cold antibodies tended to move in the fastest-running γ-globulin band and were macroglobulins; one or two patients with hæmolytic anæmia secondary to disseminated lupus erythematosus showed similar peaks. Hyper-γ-globulinæmia in liver disease usually indicates chronic hepatitis or cirrhosis. Rarely a reactive hypo-γ-globulinæmia occurs, but traces of γ-globulin are always present (see Firkin and Blackburn 1958).

Conclusion

It seems probable that before long we may be able to apply on a mass scale new methods for the study of serum-proteins. These methods will most probably depend on the use of reagents more or less specific for certain components, and if reagents are stable they should permit universal application of these tests. At present proven tests are available for albumin and γ-globulin; but methods for the turbidimetric estimation of α-globulin, β-lipoprotein, seromucoid, and glycoprotein have already been described, and await either validation by other workers or modification to suit mass determinations. The benefit of modifications is exemplified by Kohn's (1957a, 1958) ultramicro electrophoresis technique, in which, by using cellulose-acetate membranes only 10 cm. long, the electrophoretic pattern of a serum can be made manifest in less than 2 hours, while it can be applied to immuno-electrophoresis with even greater saving of time and materials (Kohn 1957b).

References overleaf

FAILURE OF STERILITY IN HOSPITAL WARD PRACTICE

E. M. DARMADY
M.A., M.D. Cantab., F.R.C.P.

K. E. A. HUGHES
M.B.E., M.R.C.S.

J. D. JONES
F.I.M.L.T.

PATRICIA E. VERDON
M.B. Lond.

From the Portsmouth and Isle of Wight Area Pathological Service

CENTRAL supply of sterile instruments and fabrics for ward use is now established in many parts of the world, particularly in the United States. In this country instruments for ward use are usually boiled; and the nurses are expected to pack metal drums which are then "sterilised" in the main hospital high-pressure steriliser.

The Nuffield Provincial Hospitals Trust (1958) has lately produced an account of sterilising procedures in current use in British hospitals. In the present paper we report on bacterial standards of so-called sterile and disinfected articles, and make suggestions on how they might be raised.

Seven hospitals have been examined, the first four in association with the Nuffield team. A special observer (P. E. V.) examined in detail a number of wards in hospitals G, H, and I (table I).

TABLE I—SUMMARY OF RESULTS

Hospital	B	C	D	F	G	H	I	% contaminated
Cheatle forceps	6/27	1/4	3/8	0/18	7/28	11/23	6/25	26
Syringes	5/17	0/2	1/6	3/29	..	..	..	17
Instruments	2/23	0/6	1/9	0/9	3/30	24/49	6/43	21
Bowls, &c. } Receivers, &c. }	..	..	..	..	17/71	91/169	15/99	36
Drums	6/19	1/5	..	5/29	12/45	12/37	3/28	24
% contaminated	21	12	22	9	22	50	15	..

Denominator: number examined. Numerator: number not sterile.

Findings

INSTRUMENTS, BOWLS, AND DISHES

The standard advice given in most nursing manuals is that instruments, bowls, and dishes should be fully immersed and boiled for at least five minutes in a 2% solution of sodium carbonate or a 1% solution of sodium benzoate. In none of the hospitals was this ruling observed. Sodium carbonate solution has to be made up centrally, and none were able to overcome the difficulties of distribution. Moreover, though sodium carbonate can contribute to sterilisation, this can only be complete when carried out in a high-pressure steriliser. The usual presumption is that safety can be achieved by boiling, and it is not sufficiently recognised that preliminary thorough cleaning is essential.

TABLE II—THE CONTAMINATING ORGANISMS: RESULTS OF CULTURES

Organism	Positive cultures *
Saprophytic staphylococci	133 occasions (54%)
Subtilis group	88 „ (35%)
Chromogenic cocci	12 „ (5%)
Streptococcus faecalis	7 „ (3%)
Staphylococcus pyogenes	5 „ (2%)
Coliform	2 „ (0·8%)
Streptococcus viridans	1 „ (0·4%)

* As more than one species was isolated on a number of occasions, the total number of organisms cultured exceed the number of articles found unsterile.

To test the sterility of bowls and instruments, sterile "stick" swabs, made with non-absorbent cotton-wool, were dipped into bijou bottles of nutrient broth. The swabs were smeared over the surface of the instruments and the stick broken off into the nutrient broth. This was incubated for seven days and subcultured on blood-agar plates. (The non-absorbent cotton-wool ensured hardly any antiseptic was carried over into the culture medium.)

One reason for the inadequate cleaning was the shortage of instruments; and this was aggravated by the fact that some boilers took as long as an hour and a quarter to come to the boil. Many boilers were fitted with thermostatic controls, but the thermostats were often wrongly set, causing considerable delay. Since none of the boilers were fitted with thermometers, the operator had to rely on the turbulence of the water to gauge the temperature—an unreliable method (Timmins 1956).

The shortage of instruments and the practice of dressing rounds demand a quick turnover.

The nurse was sometimes seen to drop her instruments into the boiling water; and this lowered the temperature, particu-

DR. DISCOMBE: REFERENCES

Abdel-Wahab, E. M., Rees, V. H., Laurence, W. J. R. (1956) Ciba Foundation Symposium on Paper Electrophoresis; p. 30. London.
Albertsen, K., Heintzelmann, F. (1950a) *Acta med. scand.* **136**, 313.
— — (1950b) *ibid.* p. 316.
— Christoffersen, N. R., Heintzelmann, F. (1950) *ibid.* p. 302.
Ball, K. (1950) *Brit. med. J.* i, 1236.
Bennhold, H., Ott, H., Kallee, E. (1951) *Hoppe-Seyl. Z.* **287**, 185.
— Peters, H., Roth, E. (1954) *Verh. Dtsch. Ges. inn. Med.* **60**, 630.
Bernfield, P., Berkowitz, M. E., Donahue, V. M. (1957) *J. clin. Invest.* **36**, 1363.
Bichel, J., Bing, J., Harboe, N. (1950) *Acta med. scand.* **138**, 1.
Bøe, J. (1945) *ibid.* **123**, 101.
Bracken, J. S., Klotz, I. M. (1953) *Amer. J. clin. Path.* **23**, 1055.
Brahmachari, U. N. (1917) *Ind. med. Gaz.* **52**, 429.
Bruton, O. C. (1952) *Pediatrics*, **9**, 722.
Carballo, J. R., Lopez-Garcia, E. (1946) *Rev. clin. esp.* **22**, 356.
Christenson, W. M., Dacie, J. V. (1957) *Brit. J. Hæmat.* **3**, 153.
— — Croucher, B. E. E. (1957) *ibid.* p. 262.
Dekema, H. (1951) *Ned. Tijdschr. Geneesk.* **95**, 3774.
de la Huerga, J., Popper, H. (1950) *J. Lab. clin. Med.* **35**, 459.
Discombe, G., Jones, R. F., Winstanley, D. P. (1954) *J. clin. Path.* **7**, 106.
Fagraeus, A. (1948) *Acta med. scand.* **294**, suppl.
Faust, E. C., Meleney, H. E. (1924) *Amer. J. Hyg.* monograph series no. 3. Studies on *Schistosoma japonica*; p. 227.
Firkin, B. G., Blackburn, C. R. B. (1958) *Quart. J. Med.* **27**, 187.
Gitlin, D., Hitzig, W. H., Janeway, C. A. (1956) *J. clin. Invest.* **35**, 1199.
Good, R. A., Zak, S. J. (1956) *Pediatrics*, **18**, 109.
Homburger, F., Petermann, M. C. (1949) *Blood*, **4**, 1085.
Jacox, R. F. (1953) *J. clin. Invest.* **32**, 661.
— Gale, R. G. (1951) *J. Lab. clin. Med.* **37**, 728.
Jimenez-Diaz, C., Arjona, E., Ales, J. M., De Landazuri, E. O., Lopez-Garcia, E. (1949) *Bol. Inst. med. Res., Madrid*, **2**, 1.
— — (1949) *ibid.* p. 71.
— — (1950) *Cardiologia*, **16**, 110.
Keyser, J. W. (1950) *J. clin. Path.* **3**, 106.
Knedel, M. (1957) *Blut*, **3**, 129.
Kohn, J. (1957a) *Clin. chim. acta*, **2**, 297.
— (1957b) *Nature, Lond.* **180**, 986.
— (1958) *ibid.* **181**, 839.
Kunkel, H. G. (1947) *Proc. Soc. exp. Biol., N.Y.* **66**, 217.
— Hoagland, C. L. (1947) *J. clin. Invest.* **26**, 1060.
— Slater, R. J., Good, R. A. (1951) *Proc. Soc. exp. Biol., N.Y.* **76**, 190.
Kürten, H. (1929) *Klin. Wschr.* **8**, 1704.
Larson, D. L., Tomlinson, L. J. (1953) *J. clin. Invest.* **32**, 317.
Levin, B., Oberholzer, V. G., Whitehead, T. P. (1950) *J. clin. Path.* **3**, 284.
Mackay, I. R., Vonwiler, W., Goldsworthy, P. D. (1954) *ibid.* **7**, 855.
Pagel, W. (1949) *Amer. J. med. Sci.* **218**, 425.
Permanyer-Macia, J. J., Cañadell-Vidal, J. M. (1943) *Med. clin.* **1**, 116.
Phillips, R. A., Van Slyke, D. D., Emerson, K., Hamilton, P. B., Archibald, R. M. (1945) Copper Sulphate Method for Measuring Specific Gravities of Whole Blood and Plasma. New York.
Porges, R. F. (1956) *J. Lab. clin. Med.* **47**, 960.
Rörvik, K. (1950) *Acta med. scand.* **137**, 390.
Rutstein, D. D., Ingenito, E. F., Reynolds, W. E. (1954) *J. clin. Invest.* **33**, 211.
Schwartz, M., Thomsen, B. (1957) *Brit. med. J.* i, 14.
Shedlovsky, T., Scudder, J. (1942) *J. exp. Med.* **75**, 119.
Shetlar, M. R., Bullock, J. A., Shetlar, C. L., Payne, R. W. (1955) *Proc. Soc. exp. Biol., N.Y.* **88**, 107.
— Payne, R. W., Padron, J., Felton, F., Ishmael, W. K. (1956) *J. Lab. clin. Med.* **48**, 194.
Sterling, K. (1949) *J. clin. Invest.* **28**, 1057.
Stidworthy, G., Payne, R. W., Shetlar, C. L., Shetlar, M. R. (1957) *ibid.* **36**, 309.
Stirland, R. (1956) *Lancet*, i, 672.
Svartz, N. (1957) *Acta med. scand.* **158**, 163.
Trias de Bes, L., Riera, J., Tena, A. F. (1946) *Rev. clin. esp.* **22**, 6.
Uriel, J. (1958) *Nature, Lond.* **181**, 999.
Waldenström, J. (1949) *Pr. méd.* **57**, 213.
Wang, I. (1953) *Brit. med. J.* ii, 971.
Westergren, A., Stavenow, S. (1951) *Acta med. scand.* **139**, 214.
Wuhrmann, F., Wunderly, C. (1957) Die Bluteiweisskörper des Menschen; p. 499. Basle.

larly when the boiler was small. She was also hampered by clouds of steam obscuring her view. Instruments and bowls became interlocked, and water could no longer reach all their surfaces. Often the same instruments were picked out by another nurse within a few seconds.

From experiments with thermocouples we concluded that syringes need up to three minutes, and instruments wrapped in lint up to four minutes, to reach 90°C.

Because it took so long for sterilisers to reach boiling-point, it was often necessary for the nurses to start early in the morning if they were to prepare enough instruments for dressing rounds; and to enable them to get through their work, all the instruments were boiled simultaneously. These were laid up either in bowls or on trays and covered with a sterile towel. Continual movement of the towel backwards and forwards then led to contamination.

For example, 23 dishes, receivers, gallipots, and bowls were swabbed when first laid out on the dressing trolleys. 10 of these were not sterile, and of the remainder 6 were infected after standing for five minutes, 5 more after ten minutes, and 1 after fifteen minutes, *Staphylococcus pyogenes* being isolated twice. Only 1 was sterile when actually used.

Many bowls and instruments became covered with scale after repeated boiling, and up to three-quarters of an hour daily was needed to clean them. Organisms could be isolated from the scaly surfaces. In other wards boilers were turned on for long periods so that instruments should be ready in an emergency; and this had the unfortunate effect that some of the water evaporated.

Cheatle Forceps

Many of these were infected. Three or four pairs were often stored in one container; sometimes the level of the fluid in the containers was below the joint; and many of the antiseptics used were unsuitable. The containers were infrequently refilled and often kept on windowsills or in sluice-rooms adjacent to lavatories.

Cutting Instruments

Since boiling rapidly destroys the cutting edge of instruments, ward sisters prefer to sterilise their cutting instruments by soaking them in disinfectants. All cultures of blades previously contaminated with a non-pathogenic strain of *Clostridium tetani* and soaked for twenty-four hours in various proprietary preparations, as well as in lysol and ' Sudol ', yielded a growth.

DRESSINGS AND DRUMS

In all hospitals visited, the nurses packed metal drums with dressings or towels for use on their own ward.

To test the sterility of dressings samples of cotton-wool swabs, gauze swabs, &c., were picked from " sterile " drums with dissecting forceps previously sterilised individually in glass tubes in the infra-red steriliser. The swabs were then dropped for culture into large wide-mouthed jars containing 100 ml. nutrient broth.

There was often a shortage of drums, and many lids fitted badly. The drums were sent to the hospital sterilisers, and then returned to the ward. The two to three hours taken by the steriliser to operate aggravated the shortage of drums. On a number of occasions it was noticed that the slides had not been closed, and that there was nothing to indicate whether the drums had been in fact sterilised.

On busy wards the lid of the larger drums might be opened twenty times a day. Most wards lack storage accommodation, with the result that drums are placed in unsuitable places—on the floor or opposite an open window. On medical wards 4 or 5 drums were sometimes in use at the same time, not in rotation.

It was possible for a drum to be on the ward for up to ten days, and for the dressings to become quite heavily contaminated.

TROLLEYS

Since the boiler may take time to come to the sterilising temperature, the dressing trolleys may be laid up an hour or two before the dressing round. On occasions this clashes with the end of the sweeping round. At other times all the available instruments are laid up on a single trolley, together with a generous supply of sterile dressings. This trolley is then covered with a sterile towel, and wheeled from patient to patient. As soon as a dressing is completed, the used instruments are returned to the steriliser for reboiling. In this way time is saved, but the instruments and dressings become progressively infected.

This technique probably accounts for the high contamination-rate in hospital H. In hospitals G and I the trolley was relaid after each patient. This method, however, was time-consuming, and sometimes led to waste of dressings, because the nurse could not forecast the amount that would be needed.

Another practice which resulted in contaminated dressings and instruments was laying a trolley many hours in advance of the doctor's visit: the prepared trolley was covered with a sterile towel, but often inadequately. Overcrowding and the faulty siting of the sterilising equipment in relation to the sluice-room also contributed to contamination.

Because of overcrowding dressings were often carried out in the only available space—the sterilising room. The removal of the patient's clothing led to an immediate bacterial aerosol. Dirty dressings were deposited in bins which were frequently kept in the sterilising-room.

The siting of boilers is often dictated by the space available; and it is therefore not surprising that in two of the hospitals sterile dressing trolleys have to be laid up in the immediate neighbourhood of the sluice-room.

BEDPANS

The Medical Research Council memorandum, the Control of Cross Infection in Hospitals (1951), recommends that bedpans should be disinfected by heat. The usual method is to discard the solids by means of a sluice or washing-machine and to boil the bedpan in a tank. We noticed, however, that few of the washers removed all the fæcal material, and that in the large tanks the water took a long time to boil. Cultures of the adherent material yielded positive results even after boiling for five minutes. Sometimes the pans were withdrawn before they had been sufficiently heated, and often they were placed in the boiler during the heating-up or boiling period, thus taking the water off the boil.

Various methods of sterilising were used in the wards:

1.—The bedpan is emptied and later washed with water by hand.

2.—The bedpan is washed in a special washer and subsequently boiled.

3.—The bedpan is placed in a special washer, fitted with cold and hot water for flushing and with steam for disinfection. Hand controls are fitted for each process.

4.—Automatic bedpan disinfector, type I, fitted either to the main water-supply or to a special cistern 18 ft. from the ground with either hot or cold water. Steam is supplied

TABLE III—CONTAMINATION OF BEDPANS AFTER VARIOUS METHODS OF STERILISATION

—	No. of samples	No. of isolations of fæcal organisms
Sluice only	93	93 (*100%*)
Hand operated washer with steam	48	48 (*100%*)
Sluice and boiled	18	11 (*60%*)
Automatic apparatus, type I	66	34 (*51%*)
Automatic apparatus, type II	173	71 (*41%*)
Type II automatic apparatus fitted with high-pressure wash	12	3 (*25%*)

through the same flushing nozzles. The cycle is set to give a twenty-second flush with water and a thirty-second flush with steam.

5.—Automatic bedpan disinfector, type II. The pan is flushed with warm water by means of a special pump followed by injection of steam for thirty seconds.

6.—Automatic bedpan disinfector, type II, fitted with improved high-pressure pump, but with the same steam cycle.

Though no guarantee could be given that these procedures had been properly carried out, we tried to determine their efficacy, taking swabs from six bedpans at weekly intervals (table III). A further trial was carried out to determine the presence of staphylococci (table IV).

TABLE IV—CONTAMINATION OF BEDPANS WITH STAPHYLOCOCCI AFTER VARIOUS METHODS OF STERILISATION

—	No. of samples	No. of isolations of staphylococci
Sluice only	35	3 (*8%*)
Non-automatic	24	0
Automatic, type I	34	0
Automatic, type II	31	0
Sluice and boiled	18	0

The failure to disinfect bedpans can be traced to a number of causes.

1. The flushing process may be inadequate, either because the jets are wrongly placed or because the force of the water is insufficient.

2. On the British Standards Institute (B.S.I.) bedpan the flange or seat is turned inwards, and most flushing machines force the fæcal material to the undersurface of the flange where it adheres. As such pans are not fitted with handles, most nurses cover them with a cloth and hold them by the flange. On other bedpans, not of the B.S.I. pattern, the front is rolled inwards and forms a lip which is sometimes perforated. This makes adequate sluicing impossible.

3. Although automatic machines go a long way to achieving disinfection, in particular of staphylococci, complete safety cannot be obtained. The reason may be either inadequate flushing or too short a steam cycle. This was noticed particularly during the trial of automatic bedpan disinfector type I, where new stainless-steel bedpans (B.S.I. pattern) were introduced in place of anodised aluminium: the contamination-rate, instead of falling, increased. Investigations in progress suggest that the steam cycle should be at least forty-five to sixty seconds.

4. Sometimes nurses polish the pans with swabs which they keep specially for that purpose, thus carrying bacterial contamination from one pan to the next.

5. In some wards the pan was not subjected to steam if it had been used only for urination.

Automatic machines with a pre-set time-cycle are essential. We found that, when the flushing machines were operated with hand controls, the time given for each cycle was considerably less than what was found adequate for the automatic cycle.

Discussion

These data clearly show that many ward procedures fall short of the required bacterial standards. We do not believe that the hospitals surveyed are any worse than others in this country—indeed, some may be better. It is obvious that an unfair burden is placed on nurses by providing them with inadequate equipment and that much nursing time could be saved by central sterile supplies.

The poor performance of most hospital high-pressure steam sterilisers has been discussed by Bowie (1955) and Howie and Timbury (1956). Quick-acting high-pressure steam sterilisers, widely used on the Continent, would increase efficiency and speed of turnover; and, though it seems unlikely that they could be made available to every hospital, hospital groups might be provided with them. The annual cost of maintaining boilers and the damage by steam to their walls are fully discussed in the Nuffield Provincial Hospitals Trust's report.

The human factor is important: those responsible for sterilisation should be taught the principles behind the methods and how they should be applied to each of the articles. The hospital engineer, the domestic staff, the doctors, and the hospital bacteriologist must share the responsibility with the nurses; and the hospital management committees, on whom the legal burden rests, must also play their part. To this end it may well be necessary to appoint regional medical advisers who would be responsible for maintaining bacteriological standards and for advising on the efficiency of high-pressure steam sterilisers and dressing techniques.

We are convinced that central sterile supplies will in the long run prove the most economical arrangement, and bacteriologically the safest.

Summary

Investigations into bacterial standards in hospital ward practice showed that between 9% and 50% of the equipment stated to be sterile was in fact contaminated.

Bedpans may be heavily contaminated. Automatic bedpan washer-disinfectors help to reduce the number infected. The British Standards Institute pattern of bedpans has an internally reflected seat which causes difficulty in sluicing. Fæcal material can adhere to the undersurface of the seat and is not disinfected by boiling.

Although improved techniques can raise the standard of sterility the ultimate aim should be to provide central sterile supplies on a group basis.

Our thanks are due to the research committee of the South West Metropolitan Regional Hospital Board for an expenses grant which made this work possible. We are also grateful to Brigadier J. D. Welch and Miss Anne Amsden of the Nuffield Provincial Hospitals Trust for their cooperation in providing samples from hospitals B, C, D, and F.

REFERENCES

Bowie, J. H. (1955) *Pharm. J.* **174**, 473.
Howie, J. W., Timbury, M. C. (1956) *Lancet*, ii, 669.
Medical Research Council, Memorandum no. 11 (1951) H.M. Stationery Office.
Nuffield Provincial Hospitals Trust (1958) Present Sterilising Practice in Six Hospitals.
Timmins, N. G. (1957) *Nursing Mirror*, July 27.

Dialogues of Today

SPECIALISTS

SOCRATES: They tell me, Eryximachus, that more doctors work in our hospitals now than ever before, and that in some hospitals there are two or three times as many as there were a quarter of a century ago. And yet there are no more patients. Why should this be?

ERYXIMACHUS: It is the result of specialisation, Socrates.

SOCRATES: Does a specialist, then, do less work than one who is not a specialist?

ERYXIMACHUS: Not at all. Let me explain. In the past a patient who suffered from a disease of the heart or lungs was treated by a physician who dealt with any disease not requiring surgery, but now there are heart specialists and lung specialists who see many of these patients. If a hospital is to be up to date, therefore, it must have a heart specialist and a lung specialist as well as a general physician on its staff.

SOCRATES: So I suppose a heart specialist is able to treat heart-diseases which a general physician cannot treat?

ERYXIMACHUS: Yes, and for that reason, as soon as one specialist is appointed to a hospital it is necessary to appoint a second of the same kind; for if the first is ill or on holiday it will no longer be possible for a general physician to look after his patients, since it is the inadequacy of the general physician for this which has led to the appointment of the specialist. And, of course, two specialists will require a specially trained assistant, who himself wishes to become a specialist, and he too must have someone to take his place if he is away, and there must be a resident doctor as well. So in the grammar of medicine the positive is "specially interested", the comparative is "specialist", and the superlative is "head of a special department".

SOCRATES: And are there specialists in medicine or surgery for every part of the body?

ERYXIMACHUS: For most of them, certainly; and it is possible to specialise in a method of treatment, which may be applied to different parts of the body, or even in the treatment of a single disease wherever it occurs, or in all diseases at some particular age.

SOCRATES: There seem to be many ways of defining a specialty, and I suppose new ones are still being established.

ERYXIMACHUS: Yes, indeed; the latest is rheumatology.

SOCRATES: What is that?

ERYXIMACHUS: It comprises all those diseases treated by a rheumatologist.

SOCRATES: I suppose a patient suffering from anæmia will be sent to the heart department.

ERYXIMACHUS: Only accidentally, Socrates, for the heart department deals with the circulation and not with the blood.

SOCRATES: But does it not sometimes happen that anæmia affects the heart as it does any other organ?

ERYXIMACHUS: Yes, and of course the cardiologist will recognise that and treat the patient accordingly.

SOCRATES: And if a tendency of the blood to clot interferes with the circulation, is not that a matter of concern to the heart specialist?

ERYXIMACHUS: Certainly, the cardiologist must know all that he can about the clotting of blood.

SOCRATES: And if the blood contains too much of some substance, so that it is deposited on the vessel walls, does that concern the heart specialist?

ERYXIMACHUS: Certainly.

SOCRATES: And so it would seem that the cardiologist is concerned with the blood so far as it affects the circulation but not otherwise.

ERYXIMACHUS: Yes, that is so.

SOCRATES: Is there then a specialist who is concerned with what the blood is in itself?

ERYXIMACHUS: Certainly. The hæmatologist's work is to know how the blood is formed and destroyed, and whether there is too much or too little of one of its constituents.

SOCRATES: He deals, then, with the blood as the nourisher of the body, and the carrier of the vital spirits.

ERYXIMACHUS: No, he is concerned only with what is visible in the blood, or what can be inferred from the behaviour of its visible parts. Its nutrient properties and the vital spirits are matters for other specialists, who deal with its invisible features, such as chemists and endocrinologists.

SOCRATES: You must forgive me, Eryximachus, if after hearing what you have said I seem more ignorant than I was before. But if I understand you aright, those who specialise in different parts of the body are concerned with the blood only so far as it affects their own specialty, while those who specialise in the blood itself are not concerned with some of those properties through which it affects the welfare of the rest of the body. Are there not some doctors who study the body as a whole?

ERYXIMACHUS: Yes, indeed, Socrates, they are the general physicians. And I can now answer your original question. Though there are now many specialists who are advancing our knowledge of medicine, there are as many general physicians and surgeons as there were before. And they are more necessary than ever, for they are specially qualified to see the patient as a whole and to teach this point of view not only to those doctors who will later become specialists, but also to the much larger number who will care for the sick in their homes.

SOCRATES: And do these experts in comprehensiveness add to knowledge as well as teaching?

ERYXIMACHUS: Alas, it is still too often thought that to do research it is necessary to be a specialist, but the very limitations of specialism are encouraging young doctors particularly to investigate those reactions of the body which are not peculiar to any single organ.

SOCRATES: But it would seem that they are handicapped by being called physicians. Let us name them holognosiologists.

ERYXIMACHUS: Excellent, Socrates; holists for short. Then they, too, will be a kind of specialist!

Parliament

N.H.S. Supplementary Estimates

ON March 12 Mr. DEREK WALKER-SMITH, the Minister of Health, said that there were four main items in the supplementary estimate of £16½ million [1] for the National Health Service in England and Wales—£8,700,000 for hospital revenue expenditure, £2,200,000 for general medical service, £2,200,000 for pharmaceutical services, and £1 million for poliomyelitis vaccine. The hospital supplement was made up of £½ million for price increases; nearly £3 million for increases in salaries and wages (£1,624,000 for domestic and ancillary staffs, £927,000 for administrative and clerical staff, and £325,000 for medical and dental staff); and just over £4½ million for acceleration of maintenance work and replacements. One of the main causes of the supplement to the general medical services was the 4% interim increase given general practitioners.

THE PRICE OF DRUGS

Turning to the pharmaceutical services, he said that the £2 million extra needed here brought their total cost to £69 million. This was admittedly a large amount, but it should be kept in perspective. It was about a tenth of the total cost of the N.H.S., and that proportion had remained constant over the past three or four years. The original estimate allowed for about 216 million prescriptions at an average cost of 6*s*. each. The present expectation was that there would be 205 million prescriptions at a cost of 6*s*. 5½*d*. each. Not only was the general upward trend of costs reflected in drug costs, but the

1. See *Lancet*, Feb. 7, 1959, p. 320.

newer expensive drugs, such as antibiotics, corticosteroids, and some cardiac preparations, now account for about 40% of the total ingredient cost of prescriptions. The cost of these new drugs must be balanced against the contribution they made to the national economy by shortening illness. The third reason for increased costs was the prescription of increased quantities, but this was not necessarily uneconomic. In chronic illness it was a proper practice and not necessarily wasteful at all. This trend was particularly marked in 1957, after the change in the basis of the prescription change, but it did not seem to have gone significantly further since. Many useful methods of keeping the drug bill within reasonable bounds had been devised. An agreement about the prices of most preparations had been negotiated with the industry to operate for a trial period. They were now rather more than half way through it and were watching its progress closely.

The £1 million for poliomyelitis vaccine was the smallest item, but it was important. At the end of 1958, over 6 million children had been vaccinated twice, and nearly 1/4 million who had had one injection were awaiting their second injection. Over 3/4 million had received a third injection. Unfortunately young adults, instead of showing the traditional impetuosity of youth, had been dragging their feet. He urged that they should come forward at once in their own interests.

Dr. EDITH SUMMERSKILL felt that the sum used by the hospital service was disproportionate to some of the other services—for example the general medical services. Only good medical administration could ensure efficiency combined with economy in the medical sphere. The Bradbeer Committee had recommended that a medical administrator should be appointed in the larger hospitals. The cost of many of the things about which the Minister had spoken would come within the purview of such an administrator. He would also supervise the medical equipment and medical supplies in cooperation with the chief pharmacist. She attached great importance to the overall authority of one person who could make decisions and recommendations in the interests of economy and efficiency.

She believed that some of the extra money needed for the pharmaceutical services was due to overprescribing. The Government had been warned that the charge-per-item would be against the interests of the patient and would not reduce the drug bill. It had in fact increased the price of the prescription and put up the drug bill. If a general practitioner was shown to be overprescribing he was asked to give an explanation. Was any examination made of the prescribing costs of consultants in the same specialty in different hospitals, particularly in relation to outpatients? The market was still being flooded with new proprietary drugs, and the Minister had had questions put to him from both sides of the House about the high charges made by American firms operating in this country. She asked the Minister to respond to the repeated request for an inquiry into this aspect of the service.

Mr. MAURICE EDELMAN said that the whole onus of cutting down the cost of the pharmaceutical service was being laid upon the doctors. So far from the doctors being at fault, the responsibility for the substantially increased cost, particularly in proprietary medicines, lay in the fact that these drugs had fallen into the hands of a ring of producers who were demanding of the consuming public prices which, if they were translated into terms of other products, would cause a tremendous wave of protest all over the country. He agreed that companies which developed pharmaceutical products which were the result of many years of research were entitled to recoup their research costs. But it was utterly wrong that any company should derive from the public a profit of 1990% for a corticosteroid drug when it was possible for a comparable drug to be produced considerably more cheaply. He believed that the country was being held to ransom by the pharmaceutical industry working in a tight ring. Had the Minister investigated these matters with a view to submitting his conclusions to the Restrictive Practices Court?

Sir HUGH LINSTEAD believed that few industries were more closely scrutinised than the pharmaceutical industry. In his opinion, less than justice had been done to the Ministry of Health, the British Medical Association, and the Pharmaceutical Society of Great Britain for the publication of the *British National Formulary*, which had had a remarkable effect in keeping down the cost of drugs in this country. In Canada and the United States about 90% of the prescriptions were proprietary medicines, whereas in this country the figure was about 50%.

He suggested that the present shortage of pharmacists could be remedied by the creation of a group pharmaceutical service. It need not necessarily mean an increase in cost, because the need was possibly for fewer and better-paid pharmacists and a better and more organised use of technicians, rather than a substantial increase in the number of pharmacists. He hoped that the Minister would not delay any longer his decision on what he wished to do with hospital pharmacists and what he would do with the other medical auxiliaries dealt with in the Cope report.

SOME OTHER PROBLEMS

Mr. PERCIVALL POTT spoke of the difficulties of small maternity units in rural areas in obtaining enough trained midwives to keep open. Mr. WILLIAM GRIFFITHS pointed out that in the Manchester area it was more difficult for expectant mothers to get a bed in a maternity ward than it was seven years ago.

Dr. DONALD JOHNSON had been interested by the new hospital costing returns and strange anomalies they showed. The cost of one hospital outpatient attendance, for instance, worked out at 17*s*. 6*d*., which was almost as much as a general practitioner was paid for attending a patient for a whole year.

Mr. DENIS HOWELL was concerned at the definite move everywhere for whole-time consultants to change to maximum part-time consultant work. He was a member of the management committee for Marston Green Maternity Hospital which had never had a single pay-bed. There was a sudden recommendation that there should be four. Why were they wanted? The reason was that the consultant gynæcologist suddenly decided to transfer from whole-time to maximum part-time service, and said, "If I have not any pay-beds for patients there is not much point in my transferring". So, for the first time, the committee had decided that in Marston Green Hospital there should be four pay-beds.

RESEARCH AND THE N.H.S.

Mr. JULIAN SNOW suggested that the Minister should accept normally the element of research payable to a patent-holder of a drug as about 5–6% on the sale price. He drew the Minister's attention to the regrettable lack of basic pharmaceutical research in this country. Although the Minister might say that research was not the province of his department, it was inevitably his responsibility, bearing in mind that the National Health Service was by far the greatest single customer of pharmaceuticals in the world. In the long run we were paying for patent rights held outside this country. If we had spent more money in the past in pure research, there would not be this leakage of hard currency.

Mr. RICHARD THOMPSON, parliamentary secretary to the Ministry, said that medical and nursing teams from his department would visit the areas where the shortage of midwives was most acute to advise on remedial action and obtain more information on local difficulties, as a guide to future policy. The Minister had been advised that if a consultant, with the agreement of his board, changed from whole-time to part-time work and there was no substantial change in duties, there was no need to advertise the post. In this matter the Ministry had an agreement with the medical profession and it would be inadvisable to seek any modification or adjustment of that while the Royal Commission was still sitting.

Turning again to the pharmaceutical services, Mr. Thompson said that they were faced with two questions—whether prescribing was extravagant and whether we were paying too much for the drugs. *Prescribers' Notes* were issued to doctors and the *National Formulary* to all clinical students and hospital doctors. Committee reports and other information were circulated regularly. The Ministry were trying to keep the need for economy in prescribing constantly before all doctors. The Minister was closely concerned to ensure that reasonable prices should be secured for new drugs after the three-year period. The scheme would be reviewed before it ended to see whether it could be improved.

On the question of American subsidiaries, he would say that if new drugs were not manufactured in Britain, the alternative was to import the finished product; and that was always more expensive. It was not right to think of these firms as plunderers. Foreign firms had sunk considerable sums in setting up appliances here and we derived a valuable export trade and thriving industry from it, apart from the benefit to the National Health Service of having these drugs which would otherwise be unobtainable from home production. The drug industry was spending about £4 million annually on pharmaceutical research.

Last year the Minister had mentioned his intention to create a body to assist in the development of efficient techniques in the N.H.S. Sir Ewart Smith had agreed to serve as chairman of the council which the Minister was now setting up. One of the first problems which, no doubt, the council would wish to consider was the best method of extending efficient studies in the Health Service. The Ministry would shortly be issuing guidance to hospital authorities designed to improve the methods of selecting candidates for administrative appointments. The present manpower control in respect of non-medical staff of hospitals was to be removed and hospital authorities were to be given wider delegated powers. A small team was to be set up in the Ministry to visit hospital authorities and report on their staffing situation in order to facilitate the spread of good management practices and promote the economical use of staff.

A supplementary estimate of £2,376,500 was introduced for the National Health Service in Scotland.

Home Office Estimates

The Estimates for the Home Department, Law, and Justice for 1959-60, which were published on March 12, allocate £14,700,000 for prisons in England and Wales (compared with £11½ million in the current year). Of the £3 million increase, slightly over £2 million will go to provide additional prisons, borstals, detention centres, workshops, and staff quarters, and on improvements. Other increases include: £114,000 towards probation, £10,800–£15,000 for research into the causes of delinquency and the treatment of offenders, and £8000 for grants-in-aid for marriage guidance.

Lord STOPFORD OF FALLOWFIELD, the second medical life peer, took his seat in the House of Lords on March 10.

QUESTION TIME

Recruitment to Colonial Medical Service

Mr. ARTHUR BLENKINSOP asked the Secretary of State for the Colonies what medical posts in the British West Indies calling for recruitment from Great Britain remained unfilled.—Mr. JULIAN AMERY replied: Vacancies number 32; and 6 candidates have so far been selected against them. Mr. BLENKINSOP: Is the Under-Secretary aware that there is very great anxiety about the lack of recruits coming forward, and would he not do something both to review the financial terms of the appointments and also look at the possibility of joining the Colonial Medical Service in some way with our own National Health Service in order to give some greater sense of security to those who apply? Mr. AMERY: I will certainly look into the proposal.

In England Now

A Running Commentary by Peripatetic Correspondents

PEOPLE who write up series of cases seem to fall into two categories—those who just scrape together as many cases as they can lay hands on, regardless of their number, and those who set themselves a definite target and go on collecting until they reach it. That the usual target is 100 cases is understandable enough; nor is it surprising, human patience being limited and the struggle for priority keen, that some give up at 98 or even 99. What does strike me as curious is that so many, having achieved their century, spoil the look of the thing by adding just one more. Of course, 101 may have been a peach of a case, just crying out to be included, or some officious and meddlesome editor may have discovered a flaw in the author's arithmetic at the last moment. But I suspect that what more often happens is that when the author submits his paper on *The Results of Pinealectomy in 100 Cases of the Pecksniff-Tuttlebury Syndrome* to some hardbitten expert for an opinion before trying it on an editor the conversation runs something like this:

Author (eagerly): Well, what do you think of it?

Expert: Not bad, not at all bad—apart from your statistics of course.

Author: But I thought my figures were pretty good. They're almost as good as Bloggs', anyway.

Expert: Oh, I daresay. But just look at them—mortality 7%, complications 20%—do you realise there's not a decimal point from start to finish?

Author: I know. That's the whole beauty of having exactly 100 cases; none of those frightful calculations.

Expert (shaking his head disapprovingly): Very shortsighted policy if you don't mind my saying so, old man. Nothing like a bit of mathematics to impress the customer, you know. He'll think all these round numbers are a bit too good to be true.

Author (crestfallen): Oh, dear! What do you think I'd better do, then?

Expert: Why not cut out a few cases? Knock your total down to some nice awkward figure like 93 or 87.

Author (to whom every case is a cherished collector's piece): Oh no! I could never do that!

Expert: Well, what about adding a few on, then?

Author (doubtfully): I *could* include old Mrs. Soandso, but we only did her last week and she's a bit dicky.

Expert: Better get her in quickly, then, before she can put your mortality-rate up. As it is, she'll bring it down.

Author (warming to the idea and getting busy with paper and pencil): My word yes, with 101 cases it would be only 6·93%—that's *much* better. Why, even Bloggs' mortality was six point something. And the complication-rate—.

Expert: I shouldn't overdo it, old man, if I were you. Why not just say "complications occurred in less than 20% of cases"?

* * *

Last night my telephone rang and an unknown American asked for me.

"Gee, I'm your cousin," she exclaimed triumphantly, and began to describe how she and her husband had traced me, a descendant from a common ancestor. In the middle of winter they hired a car and "toured the whole island" in their search, covering 8000 miles (and visiting most of the well-known beauty spots on the way). They traced the village where my great-grandmother had settled after leaving America as the result of a scandal—which, my cousin said, was connected with her own great-grandfather. They had searched parish registers for married names and made long and often fruitless journeys to interview people who might help them. They had found the house in which I was born and the school I attended. Deep in the country they bewildered my ancient uncle, who was too deaf to understand them. Finally the trail led to me, a related "islander".

I was impressed. I had never considered myself an "islander" before, and the idea appealed to me. Moreover, my own days are spent in research, but not with the vigour, pertinacity, and ingenuity that this showed. "Do come to supper," I said. It seemed the only thing to say although ours was already on the table. Half an hour later they arrived.

They were two charming young people, flushed with the excitement of discovery. We happily shared a chicken and two bottles of wine. At midnight I drove them to the station, and they left their address and an enthusiastic invitation to come and stay in Virginia.

We have new ideas for our own holidays. Virginia is far away, but France, Italy, and Spain are nearer. We could go investigating for ourselves, and who knows where it might lead? After all, like the people who may offer us hospitality, we are descended from the Common Ancestor.

* * *

When first we were cajoled by an energetic registrar into making placebos, we shrugged our shoulders and talked darkly of having better things to do with our time. But when Sister came and complained that our tablets were producing nausea, constipation, and ringing-in-the-ears in some of her toughest patients we began to wonder whether, after all, there might not be some latent virtue in lactose, just as there used to be in iodine socks. And, on reflection, those lactose tablets did help to keep the devouring rust away from our expensive but idle tablet machine.

When, with increasing confidence in human credulity, we turned our attention to capsules, we discovered that tablets had been mere child's play. With a common-looking white capsule, for instance, we could stop a man throwing a fit, though he might continue to grumble about his lack of sleep. On the other hand, after swallowing a red capsule, our prize insomniac slept like a babe till ten next morning, blissfully unaware of the usual aubade from trays and sterilisers. After a blue one, the hypertensive, ready to blow his gasket, grew calm and collected. And all these pharmacological prodigies for the price of an empty gelatin capsule and fifty milligrammes of starch, mind you.

Naturally, it didn't take us long to tumble to the idea that there must be money in it somewhere. So if ever you get a chance to invest in Placebo Products (Piltdown) Limited, don't hesitate. You'll be on a Good Thing—and so, I fancy, will the Minister.

* * *

I was waiting in a bus-queue in Tottenham Court Road. It was a long queue and it took four buses, coming slowly and going quickly, to reduce the numbers to a hopeful handful. We were all very patient, save a young man two in front of me, who attempted to board the fourth bus against the wishes of the conductor. He leapt on and was pushed off, but persisted in his efforts as the bus shot away, and was still valiantly trying as the bus disappeared into the distance. The old man directly in front of me turned with a sigh and said:

"That's how my old dad got the cancer, y'know."

"Really, through catching a bus?"

"No, by missing one. Did what that bloke was doing, y'see; only 'e weren't so hagile, y'see; fell and 'it 'isself in the stummick. That give 'im the cancer."

"Came on suddenly, did it?"

"Very. Took 'im off in a week. Mind you, 'e'd 'ad it on 'im for years and years. It was the fall as set it off, y'see."

"You don't suppose that he was suffering from an ulcer?"

"Oh dear, oh dear no! I know all there is to know about hulcers. Got a couple meself. No, y'see. There's three things you can 'ave wrong with yer stummick: there's caricoma . . . that's cancer to you . . .; there's hulcers; and there's a tumour. Got it? Right. Now the tumour's all right, and the hulcer's all right, so long as you treat it proper; but the cancer, that's bad, that'll get you if you don't watch it."

At this point in the lecture a bus bore my mentor away. A pity, I might have learnt a great deal more. But, at any rate, I now always take great care when boarding buses.

* * *

In the Garden—IV.

PARDON MY PRONUNCIATION

The British Genius
Seldom manifests itself in growing Gardenias,
Though acknowledged to be smellier
Than the Camellia.

Letters to the Editor

MENTAL HEALTH BILL

SIR,—The present administrative malaise, especially in mental hospitals, arises from lack of clear authority and responsibility, and from the appointment to senior positions of people whose academic qualifications and drive are not equalled by their ability to coordinate and to manage an institution.

The principles of organisation and management are fairly definite, and include a line of authority-plus-responsibility downwards from one man in full charge. Why should the mental hospitals substitute for this the administrative muddle which results from government by committee, lack of personal responsibility, and ill-defined authority?

I am not a medical superintendent, but I fail to see why Urwick's principles of organisation and management should be considered totally irrelevant to the running of a mental hospital. If selection boards were wary of appointing energetic dogmatists to senior positions, and if they included the qualities of tact and diplomacy in their requirements, there might be better staff relationships. I have seen excellent men, full of drive and reforming zeal, whose best ideas for upgrading the mental hospital were frustrated by their talent for putting people's backs up. Instead of a well-run organisation one found sometimes rage and always chronic discontent.

All this is not good for the patients. The personality deficits of those in charge can be decisive in offsetting whatever progress is being attempted in other directions.

In the hospitals at present there are several "authorities" whose inter-relationships fail to provide that strict definition required to avoid muddle and waste.

The hospital secretary, the chairman of the management committee, and the medical superintendent vary in their co-ordination from hospital to hospital. Lack of communication up and down the line is also frequently found. What appear to be arbitrary decisions are handed down centrifugally and are found in the event to be less than good, partly because those who have to work with these decisions were not at any time allowed to express their views. Often those doing the actual work can see problems invisible to the remote-control people, and thus could assist them in arriving at the best arrangements.

Let us reconsider the proposed abolition of the medical superintendent.

A medically qualified chief administrator is just as useful as a militarily qualified field-marshal; a lay field-marshal is just as undesirable as a lay medical superintendent, be he called hospital secretary or management committee chairman. And there is no intrinsic reason why the medical superintendent should not maintain excellent relationships with the other consultants. If they cannot get on with each other, this may indicate that the selection board has blundered, or that insight therapy (self-applied) is called for, rather than blaming "the system".

Let us be clear. Either we appoint really suitable medical superintendents, with management abilities and authority commensurate with their responsibility, or we ignore the whole subject and continue with an ill-defined arrangement which violates the principles of administration and tends to promote inefficiency and lack of responsibility. Perhaps it would be more merciful to "murder the horde-father" (as "Analyst" put it in his letter of Feb. 28) than to preserve an unhappy being resented by his senior colleagues, shuttled between the

chairman and the hospital secretary, responsible for what goes wrong in the hospital, but deprived of sufficient authority to maintain efficiency.

ANOTHER CONSULTANT PSYCHIATRIST.

CHILD HEALTH AND CHILD PSYCHIATRY

SIR,—Dr. Mildred Creak is to be congratulated on her important and stimulating West lecture in your issue of March 7. There will be general agreement among children's psychiatrists with most of her conclusions. Certainly we need more children's psychiatrists, certainly the standard must be raised, and certainly the training of students and graduates in child psychiatry must be more carefully planned and carried out. But the unresolved question is: what sort of training should be given to the would-be specialist in child psychiatry?

Dr. Creak appears to believe that a personal analysis is more or less essential. I would not presume to disagree, but how is Dr. Creak going to convince those outside psychiatry that she is right? One frequently hears the charge levelled that psychiatrists do not objectify their claims—for example, about psychopathology and the efficacy of certain types of treatment. How much objective proof can we advance that personal analysis necessarily makes one a better children's psychiatrist? It is difficult to reply in this matter simply on the opinion of those who have been analysed, for the same reason that one is not certain that priests are best qualified to judge on whether or not there is a God.

If we can get agreement about the usefulness of personal analysis three questions remain:

(1) How much personal analysis? Three years, five years, ten? When and how can we be sure that we have had enough? At what age is the psychiatrist going to be able to assume that he is "trained"?

(2) The economics of the matter are a further problem. Can anybody afford the expense of so long a period of training? Can the nation afford it—particularly since the child analyst has time to treat so few children analytically in the course of his therapeutic lifetime?

(3) It seems too much to hope that anyone can be fully trained, after qualification, in pædiatrics, psychoanalysis, adult disorders (out of which children's disorders are born), neurology, electrophysiology, psychological testing, and social psychiatry. If children's psychiatrists are to have a personal analysis, which of the other disciplines are to be left out?

When I started trying to learn about child psychiatry a slightly senior colleague told me: "The only way to learn how to treat kids is to treat them; ask questions, and learn from your mistakes. In the meantime it's up to the Old Man to stop you making too much of a fool of yourself."

I wonder if there is some truth in this?

Borocourt, near Reading. G. O'GORMAN.

FIFTY YEARS OF THE SCHOOL HEALTH SERVICE

SIR,—We were delighted to read Dr. Fry's letter (Feb. 14); and we fully support his views.

We approached our local medical officer of health in December, 1957, with a proposal that, as a local experiment, we should give our child patients their routine inspections. After consultation by the M.O.H. with the chief education officer we had a reply in the negative; the reason given was that it was not practicable "within the terms of Section 48 of the Education Act, 1944, and the definition of 'medical inspection' and 'medical officer' in Section 114 (1) of the Education Act, 1944". The M.O.H. suggested that such a fundamental change should be tackled by taking up the matter either with the College of General Practitioners or the B.M.A.; and that it would be impossible to gain the cooperation of individual local education committees without their first having a recommendation from the Ministry of Education about the matter.

MARGARET DUDLEY-BROWN
York. L. JOAN LETTY.

SEX-REVERSAL: GENETIC, CHROMOSOMAL, AND NUCLEAR SEX

SIR,—The term "genetic sex" as applied to man is used by different people with slightly different meanings. To most it means the sum total of all the sex-determining factors inherited by the individual at the time of zygote formation, and the term corresponds to that of "zygotic sex".

"Nuclear sex", as determined by Barr's technique, is not to be equated with the "genetic sex". The "nuclear sex"—i.e., the high or low frequency of "sex-chromatin" in resting somatic cells—allows us to infer whether an individual carries, or does not carry, two X chromosomes. This inference has cytological support as well as non-cytological help from studies of sex anomalies. In individuals whose nuclear sex is feminine (chromatin-positive) "nuclear sexing" does *not* tell us, however, whether the two X chromosomes presumably present are normal in their genic constitution or arrangement. Nor does it tell us whether there are additional sex chromosomes or whether there are autosomal anomalies of any kind that might be responsible for anomalous "sex balance" (if it is assumed that the balance theory of sex determination applies also to man) and hence anomalous sex determination. In chromatin-negative individuals (male "nuclear sex") it gives no positive information either about their sex chromosomes (XY, XO, &c.) or, naturally, about their possible sex-determining autosomes. This does not detract from the unique value of "nuclear sexing" both as a practical clinical procedure and as a screening test for fundamental biological work on sex determination and differentiation.

By "chromosomal sex", one would legitimately suppose, is meant the constitution of an individual in terms of his/her sex chromosomes (X, Y) in their various possible combinations in normal or abnormal subjects. Here again it is obvious that "nuclear sexing" as usually done can supply information which is only presumptive of the "chromosomal sex", using this term with the above meaning.

The term "sex-reversal" has, I think, been used by biologists in conditions which occurred experimentally or naturally under the influence of environmental forces when individuals with the genic (and chromosomal) constitution of one sex appeared (and functioned) as members of the other sex. Therefore, when applied to human sex anomalies, it implies a genic and chromosomal sex constitution normal for one sex, in the face of somatic appearances that are more or less nearly normal for the other sex. But in these anomalies the term "sex-reversal" has been employed to denote a discrepancy between *sexual phenotype* (generally external genital appearances) and "*nuclear sex*" of the patient. As pointed out above, "nuclear sex" cannot unreservedly be taken to represent the constitution of the individual as far as sex-determining factors are concerned. Therefore the term "sex-reversal" has no biological meaning when applied, on "nuclear sexing" grounds, to humans with sex anomalies. It only reflects what the worker who uses the terms *believes* to be the genetically determined constitution of the individual from the sex point of view and the postulated mechanism(s) of the aberration. In so far as these sex aberrations may be genetically determined by qualitatively or quantitatively abnormal "sex-genes" or chromosomes, it would not be correct to rely on "nuclear sexing" and to describe the sufferers as "genetic males" or "genetic females". These terms would have no meaning in comparison with the normal genetic influences on sex determination: "sex-reversal", in a biological sense, could not be said to have taken place.

It must be admitted that a term describing a group of conditions with a discrepancy between apparent sex and "nuclear sex" has clinical usefulness, and some workers have preferred to speak of "sex-inversions" in these cases. Unfortunately this term appears to have been used on occasions synonymously with "sex-reversal".

It matters perhaps little what term we use provided we make it clear that we do not imply exact knowledge that we do not yet possess. Words and concepts being so closely tied together, we should be careful in the selection of the first lest we create ideas that are inaccurate, may be difficult to dispel, and may impede progress and cause clinical and biological misunderstandings.

Medical Research Unit,
National Spastics Society,
Department of Child Health,
Guy's Hospital, London, S.E.1. PAUL E. POLANI.

INTERNATIONAL CERTIFICATES OF VACCINATION

SIR,—In your issue of March 7 Dr. Corbett, medical superintendent, Peninsular and Oriental Steam Navigation Company, referring to international certificates of vaccination or revaccination against smallpox, was not right in inferring that it may be possible to get the necessary forms from a local public-health authority. These authorities do not keep them. They can, however, be obtained from all the main travel agencies or direct from the Ministry of Health in London or the Department of Health for Scotland in Edinburgh.

Perhaps I should add that it is the traveller himself who is expected to get the form and take it to the doctor. There is no obligation on the doctor, or a local authority or their medical officer of health, to supply these forms.

Ministry of Health,
London, W.1. S. A. HEALD
Public Relations Officer.

PSYCHIATRIC SEMINARS FOR GENERAL PRACTITIONERS

SIR,—The Tavistock Clinic's application for recognition of their seminars, so that general practitioners attending them could claim the usual allowances, has been refused by the British Postgraduate Medical Federation.

About 100 G.P.s, many with large practices, attend these weekly groups at the Tavistock Clinic. Almost all are in National Health Service practice; most of them are married with families and have been qualified about fifteen years. Each group discusses psychological problems met by members in their daily practice. There is no formal teaching and the psychoanalyst leader refuses to accept the role of teacher or consultant. Histories are presented without notes. The doctor may have to face searching inquiry and criticism in his conduct of the case from the group. In the course of the discussion he gains insight into his own personality and sees how his own attitudes influence his work with his patients.

The great difference between this and other forms of psychiatric training lies in the fact that the leader really sees himself as coequal with members of the group. Whereas *teaching* is acceptable in most branches of medicine, it is inappropriate in the training of general practitioners for psychotherapy. The practitioner cannot learn to be a psychotherapist unless he joins the group as a doctor. If he is there as a student (though postgraduate), his reactions are those of a student; and all the discussions in the world (group or not) will not help him over the hurdle from the role of student to that of adult therapist.

I know of no other postgraduate G.P. course where work of this sort is done, and I am at a loss to understand the reasons for the Federation's decision. Provincial doctors who have applied for travel allowances (some come from Bristol, Sheffield, and Manchester) have, I understand, been referred to local departments of psychiatry. This suggests that our medical educationalists have little insight into the nature of the universal difficulties of general practice, whatever its locality. Perhaps this may be one of the grounds for public criticism from informed lay sources of the present-day role of psychiatry and mental health in terms of the public need.

London, W.13. AARON LASK.

VALLERGAN

SIR,—With reference to Dr. Cope's letter last week I should like to report details of another case of confusion following premedication with trimeprazine tartrate ('Vallergan').

A child of $3^1/_2$ years underwent tonsillectomy and adenoidectomy on Feb. 6, 1959. After premedication with trimeprazine (44 mg. 1 hour before operation) and scopolamine (gr. $^1/_{300}$ $^3/_4$ hour before), a routine operation was performed. The patient's condition was satisfactory on return to the ward after an uncomplicated ethyl-chloride/ether anæsthetic. 2 hours later 5 minims of nepenthe was given for mild restlessness. This had little effect and he became progressively more confused as the evening wore on. Nepenthe (5 minims) was repeated 3 hours later at 10.30 P.M. From then until 5 A.M. a nurse had to constantly restrain the child who was completely confused, restless, and attempting to climb out of his cot. Syrup of chloral (gr. 4) at 2 A.M. had no effect either and the child remained confused and disorientated until he at last fell asleep at 5 A.M. Next day he showed no ill effects whatsoever and made an uncomplicated recovery.

Next week another child showed mild confusion following trimeprazine premedication but not to the same extent as the first child.

In a series of over 200 cases of tonsillectomy in children using quinalbarbitone/atropine or quinalbarbitone/scopolamine premedication no cases of postoperative confusion of this degree have been encountered under similar conditions and we believe that the use of trimeprazine at least contributed to this child's confusional state.

My thanks are due to Dr. Bernard Coden for permission to publish details of this case.

Princess Beatrice Hospital,
London, S.W.5. R. B. ROBERTS.

PULSUS PARADOXUS

SIR,—Pulsus paradoxus is a well-documented phenomenon, described most frequently as accompanying constrictive pericarditis, pericardial effusion, acute hæmopericardium, mediastinal tumours, laryngeal obstruction, and asthma. I have been impressed by the frequency with which it is associated with the stertorous breathing of patients in a stupor from cerebrovascular accidents. It has been easily detected by palpation, and confirmed by sphygmomanometry, in every fatal case of "stroke" which I have observed in the past few years.

It appears usually several hours before death, before the onset of Cheyne-Stokes breathing, and may persist till death. The full pulse, and the deep stertorous respirations which these patients are likely to show, probably contribute to the great ease with which the phenomenon is detected. The paradoxical pulse is abolished when the airway is freed by pushing the angles of the jaw forward, eliminating the stertorous breathing; it recurs as a rule when the jaw is allowed to fall back. The phasic variation in systolic blood-pressure, which is usually in the range of 20 or more mm. Hg, is also abolished by this manœuvre.

The association of pulsus paradoxus with a stroke is common and ominous. Possibly the phasic variation of the blood-pressure constitutes an added burden for the damaged cerebral vasculature. Its abolition by pushing the jaw forward, or by passing an airway device, may be desirable for the vascular as well as the respiratory system.

Cátedra de Clínica Médica,
Universidad del Zulia,
Maracaibo, Venezuela. JORGE QUINTERO.

PANIC AND PHOBIA

SIR,—In spite of the troubles which afflict this country many of us have still time to read *The Lancet*. Dr. Malleson in his excellent article (Jan. 31) describes the case of an Asian technologist who developed a temperature of 102°F, with shivering and chattering of his teeth. He goes on to say that " Clinical examination failed to reveal anything suggestive of organic disease, and nothing to suggest malaria save his black skin ".

I have discussed this statement with some of my colleagues out here, who agree with me that such a picture is highly suggestive of malaria. I would go further and say highly suggestive of benign tertian malaria. Of course it would be more satisfactory to have a positive blood-film and an enlarged spleen, but even without these findings I believe the symptoms are highly suggestive. I consider that malaria was just as likely a cause of his symptoms as a psychological cause on the history as stated. In a tropical country he would almost certainly have been treated as such.

Queen Elizabeth Hospital,
Blantyre, Nyasaland. J. W. D. GOODALL.

A " CHEST SERVICE "

SIR,—The replies from correspondents to your editorial of Feb. 7 on the Joint Tuberculosis Council report on the future of the chest services, while going some way to eliminate certain misconceptions, fail to answer your final inquiry: is a " chest service " really necessary?

The existing service, founded on the old tuberculosis service, still deals mainly with tuberculosis and must provide and continue to provide a comprehensive service for that disease —i.e., for diagnosis, treatment, care and aftercare, follow-up, epidemiological inquiries, preventive vaccination of contacts, &c. Changing circumstances are now responsible for adding to these clinic duties in respect of tuberculosis an increasing proportion of work in connection with non-tuberculous chest disease. These circumstances are increasing efficiency in diagnostic work, the necessity to cater for non-tuberculous chest complications in our tuberculous and ex-tuberculous patients, and the available beds for inpatient observation and treatment. The improved diagnostic facilities are not due merely to the ready availability of chest X-rays, as suggested in your editorial. Though figures are not available for adequate supplementation of appendix 4 of the J.T.C. report—diagnosis of new cases seen at 18 chest clinics during one winter month in 1958—it can be assumed that a minimum of 25–50% of the cases referred to in that table would have been referred for consultation.

In the years to come, as the incidence of tuberculosis declines the proportion of those requiring the complete " service " of tuberculosis will decline and the proportion of work in non-tuberculous thoracic disease, comparable to that performed by the general physician, will increase. Not all non-tuberculous chest work is expected to require the comprehensive approach of the tuberculosis service. The degree of specialisation in thoracic medicine and the comprehensiveness of the service afforded for non-tuberculous disease will probably depend on the interests of the physicians concerned. In some clinics the physicians' interests will be divided between chest disease and general medicine, and full integration will slowly be achieved with general medicine as the need for the special tuberculous service declines. In others specialisation, research, and teaching may require for the convenience of patients and staff a " department " of thoracic medicine.

The pattern of evolution is surely going to depend not on the label over the door but on the quality of service provided and the keenness and efficiency of those in charge to secure maximum benefit for their patients and to advance the knowledge and practice of thoracic medicine. What is asked at the moment is that local initiative should be encouraged provided, as you, Sir, so rightly indicate, that the service in respect of tuberculosis is not prejudiced.

Churchill Hospital,
Headington, Oxford. NORMAN ENGLAND
Chairman, Joint Tuberculosis Council.

THE CHILD WHO DISAPPOINTS

SIR,—Any teacher who wanders from time to time into the worlds of other professions also concerned with children finds that statements are being made similar to the one you made on behalf of the medical profession in your editorial last week: really, we all ought to get together —the teacher and the social welfare worker, the teacher and the probation officer, the teacher and the psychologist, and so on. Inside his school the teacher often feels this need for collaboration quite acutely. He is aware that, in the case of child after child, other (inaccessible) people have, or are capable of having, answers to important questions about the child's welfare or behaviour or history; or, indeed, that their disciplines enable them to know what questions ought to be asked.

I know that nothing is easier than to suggest the formation of yet another council or committee or association; but it really does seem that what we need is some central body drawing on all the professions concerned, devoted to discussion and research, and aiming at conclusions that should be a synthesis of all the kinds of insight and experience that are involved. Not only would each group be rescued from its rather ridiculous isolation, but together we would certainly make discoveries that are beyond the reach of any one of us working alone.

Barnet, Herts. EDWARD BLISHEN.

DIETARY FATS AND ATHEROMA

SIR,—Although I am sympathetic to the stimulating ideas of Dr. H. M. Sinclair on the role of the essential fatty acids, I cannot let certain statements in his letter of Jan. 31 go unchallenged.

The statement that much separated milk is wasted is not true for this country. The percentage utilisation of skim milk in England and Wales during the year ended Sept. 30, 1958, was: powder 40, condensed 14, stock feeding 36, standardising and other purposes 10.[1] A little may be wasted over the peak of production (2–4 weeks in May and June) because it is not economic to buy and maintain the necessary machinery and transport throughout the year to handle the peak excess for such a short time.

The idea that milk and dairy products are dangerous for humans will require much more experimental evidence before it is generally accepted. As far as the dietary fat hypothesis is concerned the only irrefutable fact in the confused maze of experimental evidence, theory, and speculation is that the cholesterol, &c., level in the blood can be influenced by the type of fat fed for a short period.

1. Milk Marketing Board. Personal communication. 1959.

Unfortunately the attack on animal fats has induced the idea in uncritical circles that animal fats, among which milk fat has been singled out for special mention by Dr. Sinclair, are "saturated and therefore bad", while vegetable fats and oils are "unsaturated and therefore good". This conception is not true for the United Kingdom.

The quantities and chemical properties of fats consumed in this country are given in the accompanying table.

PROPERTIES OF THE MOST IMPORTANT FATS CONSUMED IN THE U.K. [2–4]

Fat	Production or import (000 metric tons)	Average iodine value	Saturated acids	Mono-unsaturated (oleic, &c)	Poly-unsaturated (linoleic, &c.)
Coconut ..	107	8	90–94	5– 8	1– 2
Palm kernel	135	18	75–91	11–18	1– 2
Cow milk ..	360	35	50–68	32–40	4– 6
Ox and sheep	..	42	45–58	39–50	3– 5
Human milk	..	50	46	42	12
Human depot*	..	..	26–39	42–52	10–13
Palm ..	205	50	40–50	40–50	5–11
Pig (lard) ..	..	65	25–59	40–60	1–15
Ground nut	130	90	15–20	45–64	17–38

* Included for comparison.

The average iodine value for the four main vegetable oils *unhydrogenated* is about 42, while that of the three main animal fats is about 48. In view of the fact that much of the vegetable and other highly unsaturated oils are hydrogenated, which according to Dr. Sinclair's own theories largely devalues them, there is no case for asserting that animal fats *as used in this country* are inferior from this point of view to vegetable oils.

We consume about 15 g. milk fat, 16 g. butterfat, and 4 g. cheese fat daily, equivalent to about 35 g. total milk fat daily. In addition, we take about 15 g. treated vegetable fats (mostly margarine), 49 g. other animal (mostly pig, beef, and mutton) fat, and 9 g. other vegetable fat daily. Thus, of the 108 g. daily fat intake about 84 g. is animal fat, but it is doubtful if this fat is significantly more saturated than the vegetable fat *as consumed*.

Cow milk fat is not so very different from human milk fat, so that Nature's idea of what is the best fat for human infants is not so very different from cow milk fat. Moreover, our knowledge of the fatty acids is far from complete,[2] and the analytical methods often suspect.[5] To condemn milk and dairy products outright is justified neither by the experimental evidence nor by an impartial examination of the physiology and chemistry of the problem. Much of the biochemical work has been done with very few subjects for very short times, and properly controlled long-term experiments are badly needed. It is true that a few people cannot digest or take ordinary milk, and that by far the greater nutritional value of milk lies in the solids-not-fat fraction.[6–8] The reason for the difficulty in assimilation is nearly always due to the casein content (higher than in human milk), and this is clearly shown by the fact that simple modifications leading to soft curd formation improve digestibility.[9] This is the basis for the "soft curd" milk so popular in the U.S.A.

It may be true, as reported from time to time, that certain individuals are able to assimilate vegetable but not cow-milk fat, but such cases are exceedingly rare in this country. Milk fat is very well emulsified and is liquid at body-temperature. Examination of the experimental evidence in many countries on the relative digestibilities of cow-milk and vegetable fats shows that neither is consistently superior. There is an instinctive dislike among all sections of the community of unnecessary alteration to our basic foods, and this applies particularly to dairy products and bread, which are our two most important basic foods. Special highly unsaturated vegetable oil-separated milk products may well be advisable for certain clinical conditions, but it will require much more convincing evidence before the British public in general will abandon its faith in and liking for genuine dairy products.

The natural fat in dairy products is less dangerous than the considerable quantity of hardened vegetable fats which we consume in fried foods, margarine, ice-cream, &c., if we accept either the essential fatty acid or the saturated/unsaturated fatty acids ratio theory as the underlying cause of human atheroma. If there is anything in the essential fatty acid theory it would be more practicable and acceptable to the public to increase the national intake by using more highly unsaturated vegetable oils in other foods—e.g., margarine and compounded fatty foods—and to leave milk, butter, and cheese alone.

London, W.1. J. G. DAVIS.

2. Hilditch, T. P. The Chemical Constitution of Natural Fats. London, 1956.
3. Schwitzer, M. K. Margarine and Other Food Fats. London, 1956.
4. The Facts about Margarine. London, 1959.
5. Shorland, F. B. The Minor Fatty Acids of Butter Fats. See *Dairy Sci. Abstr.* 1957, **19**, 167.
6. Kon, S. K., Henry, K. M., *in* A Dictionary of Dairying. London, 1955.
7. Kon, S. K. Milk and Milk Products in Human Nutrition. F.A.O. Nutritional Studies no. 17. Rome, 1959 (in the press).
8. Davis, J. G. *J. Soc. Dairy Tech.* 1958, **12**, 28.
9. Davis, J. G. *Dairy Ind.* 1958, **23**, 268, 496.

SUPPLY AND DIETARY USE OF FATS

SIR,—It is very necessary to take up the points in Dr. Sinclair's letter (Feb. 28), as such important principles are at stake.

Since the time factor is clearly the crucial determinant of whether any given substance in an organism's environment is to be regarded as natural or unnatural—that is to say, of whether the organism is likely to be evolved to cope with it or not, as elaborated in my earlier letters,[1] then Dr. Sinclair's argument that mutton and beef fat are not natural to us cannot stand up to serious scrutiny.

For example, he states that sheep have existed in England for not more than a third of man's existence here. To take this statement at its face value, in that case, as man existed in Europe, to which England was then joined, during the first interglacial of the Pleistocene Ice Age,[2] about half a million years ago (and the Swanscombe skull fragments from Kent date from quarter of a million years ago), this would give man up to five thousand generations to become adapted to eating the fat of the sheep, which in any case does not differ greatly from the fat of most other animals. But the argument goes much deeper than that; for we and the sheep are both of the Old World, and who can possibly believe that in those infinitely remote times our particular ancestors were segregated at this end of the land mass of Europe and Asia, whilst those of the sheep, which Dr. Sinclair only says was first *domesticated* in Asia, were segregated at the other? In any case, a fossil sheep, *Ovis savini*, occurs in the Crag of East Anglia, before any evidence of man in the country.[3] This argument would apply exactly to the consumption of beef fat, too, there being zoological evidence of the existence of wild cattle in Britain in Upper Pleistocene times (say 100,000 years ago) and even to the consumption of milk, a practice of less, though still of great, antiquity (and as regards coronary disease, one cannot refrain at this point from quoting Morris [4]: "the trend of consumption of butter fat shows absolutely no relation"). How different from all this is the case of the sunflower, which originated in the New World, and the consumption of which, as sunflower-seed oil, only started appreciably in these islands with the rise of the margarine industry over the last century or so.

Dr. Sinclair is therefore evolutionarily on the defensive all along the line in trying to make the consumption of (for example) mutton and beef fat wrong and that of (for example) sunflower-seed oil right. And this would be true, too, if he made the consumption of these unnatural fats additive rather then substitutive. For in that case he would be trying to make

1. Cleave, T. L. *Lancet*, 1958, ii, 1125, 1371.
2. Oakley, K. P. Man the Tool-maker; 3rd ed., p. 5. London, 1956.
3. Watson, D. M. S. Personal communication.
4. Morris, J. N. See *Lancet*, 1957, i, 410.

the body eat more fat than it wanted to do. Quite apart from all the evidence marshalled by Prof. Ancel Keys in favour of the quantity, as opposed to the quality, of fats consumed being the factor concerned in the production of coronary disease, there is the infinitely more important fact that the consumption of fat in excess of the body's desire for it would involve departing from evolutionary principles even more unmistakably than in the substitutive case.

Dr. Sinclair falls into a great trap if he argues from the inability of the tongue always to distinguish between butter and margarine. The sense of taste is only a reliable guide to what should be eaten, or not eaten, if it is exercised on substances to which it is evolved to be a guide—that is, on those occurring in the natural environment of the organism. Contrast, for example, the remarkable protection of the tongue against the eating of poisonous plants with its defencelessness against the taking of arsenic, which comes from the mines. But, as a matter of fact, the tongue is often not even allowed to contribute any help it could over the consumption of these unnatural fats and oils. Often the taste of these substances, which is frequently unpleasant, is largely removed by processing treatments, and masked by the inclusion of butter and other fats the taste of which is pleasant. These strategems may hold unknown dangers. Who could have foretold the serious consequences of an excess consumption of vitamin D? Yet the tongue could have prevented these consequences, if it had been allowed to make a decision in the matter of eating the cod-liver oil and other raw materials from which these massive dosages had ultimately been derived. However, I do not contend that these unnatural fats and oils actually are dangerous nor—contrary to Dr. Sinclair's assertion—did I do so in my book. I merely contend that it is not permissible to advocate the use of these fats at the expense of the natural ones. Evolutionary principles far transcend in importance blood-cholesterol levels, which are variable in their interpretation and devious in their mode of production, and which in any case can be altered by total fat consumption.

This leads to Dr. Sinclair's reference to my insistence, in my book, on the danger of eating fats in amounts not dictated by the appetite. This occurs in these islands today on an ever-increasing scale. Fat is often smuggled into the body in fried foods, in excess of the desire for it, for the sake of the accompanying fish, eggs, or other ingredients; in chocolate and other sweetstuffs, where fat is likewise often taken in excess of desire, for the sake of the accompanying sugar (and in ice-cream, too, our consumption of which has risen from less than a million gallons in 1920 to 40 million gallons in 1951,[5] and which will undoubtedly rise further); and in other sophisticated food mixtures too numerous to be recorded here. There is no need to resort to unnatural practices to alter fat consumption whilst these gross departures from natural feeding escape attention.

Dr. Sinclair states that in my book I did not refer to the work of Professor Kinsell and others, It is true I did not do so by name—there were already 2000 references available on coronary disease at the time—but I did specifically refer to the question of essential fatty acids, quoting Morris,[4] who was reported to have said that "the only available data for the United Kingdom gave no support to the hypothesis that the population was now suffering from an absolute or relative deficiency of essential fatty acids." I also quoted Yudkin.[6]

Has not perspective, in fact, been lost over the whole subject of deficiency of essential fatty acids? Does Dr. Sinclair himself still invoke a deficiency of these acids to explain lung cancer and leukæmia[7]? When he deprecates the eggs of battery-fed hens, is the fact not important that the hatchability of these eggs, if fertilised, is not impaired[8]? If these eggs will produce young birds, do we really need the reassuring statements of research-workers to make us pretty confident that we shall not come to grief in eating them? Similarly, the results of feeding animals to some extent unnaturally, however undesirable it may be, seem unlikely to affect us much at second hand, as long as the animals themselves stay healthy. However, I only wish to point out that these dangers at second hand appear quite trivial compared to those at first hand, referred to above.

5. Board of Trade. Report on the Census of Production for 1951: Ice Cream. H.M. Stationery Office, 1951.
6. Yudkin, J. *Lancet*, ii, 155.
7. Sinclair, H. M. *ibid.* 1956, i, 381.
8. Fox, S. Personal communication.

H.M.S. *Dolphin*,
Gosport, Hants.

T. L. CLEAVE.

BIRTHS IN AMBULANCES

SIR,—One reads from time to time, especially in the London evening press, of women giving birth to children during an ambulance journey. Details are usually given of the mother's name and address and the name of the ambulance attendant who delivered the child.

Although this function is part of an ambulance man's training, is there any reason why this duty should not be treated in the strictest confidence, comparable with doctors and hospital nurses?

As all ambulance services are now administered by the various boroughs and county councils it should not be difficult to issue orders forbidding attendants to divulge this information to the Press.

I had six years' experience of this service in ambulances administered by the Police and attended many such cases. Severe disciplinary action would have been taken against any officer divulging such information.

St. Albans. T. WOODWARD.

ANNUALLY RECURRING CHRONIC SUPPURATIVE HIDRADENITIS

SIR,—When I was about 50 or 60, I think, and enjoying a summer holiday in the country, I began to suffer from intense itching soon turning to sharp pain in the right axilla. This was evidently due to the formation of minute tense cysts just beneath the skin, which could be moved slightly over them. In short, there seemed to be suppurative inflammation in the sweat (coil) glands.

With difficulty I was able to pierce two or three of the most prominent cysts with the point of a sterilised penknife. A little pus escaped and the pain instantly ceased. The other little cysts disappeared spontaneously. I thought the trouble was quite over, but in following summers there was recurrence, though with diminishing severity. The attacks came to be represented by itching only and finally ceased altogether.

The explanation seems to be that a microbic or virus infection remains in a latent condition from one year to another, and flares up to activity during the summer in connection with the normal process of sweating.

I think I have seen a reference to similar cases in the Swiss medical literature. But the disease (if I may use the term) seems not to be generally known. Dr. G. B. Dowling has kindly suggested that it is related to chronic hidradenitic ulcers.

There is something else to which I wish to draw attention. When inserting the penknife into the little cysts, I felt that I had to push the point through a thin layer of loose tissue. It is therefore extremely probable that, if the cysts had been allowed to rupture spontaneously, the pus would have entered into this soft tissue, and would have caused the formation of an ulcer. Thus by my early intervention I probably saved myself from a chronic hidradenitic ulcer.

London N.W.1. F. PARKES WEBER.

CHILDREN IN HOSPITAL

SIR,—Lord Cohen (March 14) has unaccountably failed to see that the idea that the Platt Committee was in favour of breaking up any existing large general children's hospitals was not mine (for *I* did not thus "distort the truth") but arose from his own speech in the House of Lords (Feb. 12).

His quotation (March 14) from *Hansard* seems to me to make this origin of the idea even clearer, and to confirm the accuracy of my paraphrase (Feb. 28) of what I heard him say in the debate. I am, however, quite happy to leave your readers to decide what interpretation should be put upon his remarks, and what effect they could be expected to have upon his largely lay audience.

At the same time I am glad to know that he now disagrees with an interpretation which was, I am sure, both general and inevitable.

I regret that I can see no grounds for any withdrawal or apology.

Queen Mary's Hospital for Children, Carshalton. DAVID LAWSON.

CONTAINERS AND PACKS FOR STERILISING FABRICS AND GLOVES

SIR,—Among many reports of the past few years, the recent publications by the Nuffield Provincial Hospitals Trust (1958) and the Medical Research Council [1] have confirmed the low standard of efficiency of the various sterilising methods used daily in hospitals. This fact has been known for the past twelve years, but very little had been done until two years ago to improve our existing sterilisers and the methods of preventing contamination of sterilised material.

Fully automatic rectangular high-pressure and high-vacuum sterilisers made in a few standard sizes only will be in use in many hospitals in the near future. It is, however, not sufficient to sterilise all goods satisfactorily in the shortest possible time: it is just as important to keep them sterile until they are actually used in the operating-theatre.

Unfortunately there appear to be great differences of opinion among medical authorities about the most suitable and practical containers for packing the very large variety of fabrics, instruments, and gloves used daily in hospitals—especially if no air-conditioned central stores will be available during the next few years.

Various protective covers and containers are generally used in different countries: packs in double muslin or paper wrapping (U.S.A.), nylon bags (Sweden), Konrich-filter-type boxes (Continent), and Schimmelbusch type of drums or boxes with shutters (Great Britain). Packing in cardboard boxes (as recommended by the Nuffield Hospitals Trust) is confined at present to very few hospitals. Whichever method of packing is used, safe sterilisation demands complete and quick permeation of every part and fibre by the moisture and correct heat of the steam.

Since air is heavier than steam, it is essential that steam enters the material from the top and drives the air out without forming air pockets. As the vital discharge of the remaining air even in a high-vacuum steriliser must always be from top to bottom, the basic rule should be that the steam inlet is near the top, and the large air and condense outlet at the bottom. The largest pack should not exceed 22 × 12 × 10 in. Heavy sheets and gowns must be packed separately and stand on edge to ensure thorough and quick permeation. All packs must be arranged to give minimum resistance to the passage of steam. If metal boxes with shutters are used a large number of port-holes must be provided on top and bottom, and not the usual number of small perforations on front and back, which will not allow quick steam penetration and air escape if standing upright. With a modern high-vacuum steriliser it is possible to reach the correct sterilising temperature inside the fabrics within a few minutes if packed correctly.

Most people will agree with the Medical Research Council that packs only are more suitable for the existing obsolete low-vacuum or displacement sterilisers. For high-vacuum sterilisers a well-designed filter type of metal box with a large number of perforations on top and bottom fitted with replaceable filters offers many advantages. The lid of this box may also be sealed and fitted with special spring toggle fasteners to maintain sterility of the contents for a considerable period as proved by extensive tests. As there are no shutters to be opened or closed it is very simple and safe in use. Modern high-vacuum sterilisers will probably be made in a few standard sizes only. If the internal dimensions of the sterilising chamber in a rectangular steriliser are (1) 26 × 26 in., (2) 39 × 26 in., (3) 52 × 26 in. with a depth of 26 to 39 in., and two standard-size boxes are used with maximum overall dimensions of 12 × 12 × 11 in. high for fabrics and 12 × 12 × $5^1/_2$ in. high for gloves, that would give full use of available space without waste. A large box 24 × 12 × 11 in. may be used for gowns and large sheets, but it is rather heavy when fully loaded. Non-standard-size round sterilisers especially and boxes are most uneconomical in use.

Rubber gloves are very difficult to sterilise in a displacement steriliser. Heat-resisting gloves which will stand up to repeated sterilisation at 126°C or preferably 134°C would be a great advantage since they could be sterilised together with the fabrics. The usual Billfold type of muslin cover used for wrapping one pair of gloves of any size should be standardised and made of better material. It is essential to use gauze inside the folded-back cuffs and palms, ensuring that the thumbs are up before standing the covers on edge. If the standard glove box (12 × 12 × $5^1/_2$ in.) is divided into 12 compartments it will prevent any pressure on the rubber, allowing the steam to reach every part more easily.

The protective wrapping or filter material must give a minimum resistance to steam penetration, offer good protection against breakage-dust-bacteria-contact contamination in handling, and guard against the entry of insects. The new synthetic materials with very close and even weave, made specially for this purpose, would be very hard-wearing. They possess low moisture absorption and minimum shrinkage, offering many advantages as wrapping materials or filters for metal boxes.

I should welcome any suggestions which may help in achieving safe sterilisation and overcoming the difficulties in keeping the goods sterile for a long period.

G.U. Sterilizers Ltd., London, N.W.2. PAUL ZIEGLER Managing Director.

1. *Lancet*, Feb. 28, 1959, p. 425.

WHOSE RESPONSIBILITY?

SIR,—Professor Shotton and Dr. Train (March 14) have dealt fully with the technical aspects of the M.R.C. Working Party report on steam sterilisation, and I was pleased to note that they had drawn attention to the scientific training of the pharmacist in relation to sterilisation procedures.

For many years, hospital pharmacists have acquired practical experience in the production of sterile materials of a widely divergent character, and some of them have participated successfully in the organisation of central syringe services. In drawing attention to the complexity of the problems of sterilisation in hospitals, the working party underline the need for teamwork to ensure that the correct procedures are adopted and maintained. The pharmacist is able to make a useful contribution in this field and it is unfortunate that hospital pharmacy was not represented on the working party.

The technical problems of sterilisation are reasonably well known; but the outstanding, and perhaps more difficult, problem is an organisational one. This requires coordination of the staff concerned with the pharmacist, including the surgeon, the bacteriologist, the nursing staff, and the engineer. The experience gained in the organisation of central syringe services might, with advantage, be applied to a wider range of articles including surgical dressings and instruments. Centralised production would not only ensure the adoption of a prescribed technique in packing and sterilising but it would also then be possible to devise standard unit packs of sterile dressings and even instruments to facilitate aseptic handling in the wards and theatres.

By cooperation with the bacteriologist, the whole process could be subjected to routine bacteriological control and closer supervision could be ensured under conditions similar to those adopted in the pharmaceutical industry for the large-scale production of sterile materials. Furthermore, centralisation would allow greater control to be exercised over the method of delivery of the materials to the wards and theatres where they are to be used.

Royal Free Hospital,
London, W.C.1. J. W. HADGRAFT.

DIAGNOSIS OF PLEURAL EFFUSION

SIR,—I would be grateful if you could allow me to point out that the punch biopsy needle to which you refer in last week's annotation should properly be known as the Abrams needle, after its inventor, and is indeed described as such by the manufacturers.

Middlesex Hospital,
London, W.1. PAUL MESTITZ.

NEEDLE IMPLANTATION OF YTTRIUM SEEDS FOR PITUITARY ABLATION

SIR,—We have read with much interest the description of this technique by Professor Fraser and his colleagues in your issue of Feb. 21. A similar method of implanting radio-active seeds under screen control with two image intensifiers has been employed at St. Paul's Hospital since 1955 and has previously been described.[1] From a somewhat longer experience embracing 41 cases of advanced malignant disease, both of the breast and the prostate, it is thus possible to amplify some of the observations contained in the recent article.

There can be no doubt that a substantial reduction of pituitary activity can be induced by accurate emplacement of the radioactive seeds, as demonstrated indirectly by subsequent tests of ketosteroid excretion, iodine uptake by the thyroid, and the effects of cortisone withdrawal. Similarly, subjective evidence of improvement as shown by the relief of metastatic pain and restoration of ambulant activity may be a striking feature in successful cases.

Direct proof of a response at the primary and secondary sites has, however, often been harder to adduce, particularly in cases of prostatic cancer where the primary lesion is relatively inaccessible and any radiological changes in sclerotic bone metastases are open to misinterpretation. Nevertheless it is against a combined background of symptomatic relief and the period of subsequent survival that the value of the technique can most practically be assessed, and it seems necessary to emphasise that, as in the case of simpler forms of hormone control therapy, a proportion of cases amounting to at least 25% is likely to prove entirely resistant to treatment. This fact, combined with the possible hazards outlined in the article and the continued need for substitution therapy, would seem to preclude pituitary radio-inactivation as a primary definitive method of treatment and to render the technique suitable only for advanced cases where alternative measures are either inappropriate or have failed.

Applied in this manner, our experience has indicated that a previous response, either to œstrogens or castration, often affords some indication of the likelihood of further benefit from pituitary ablation, and we regard the adoption of such measures as an important preliminary, especially in prostatic cancer. Used with discretion in the advanced relapsing disease, the technique is capable of giving reasonably satisfactory results, as shown by survivals of up to 3 years and $2^1/_2$ years respectively in isolated cases of prostatic and mammary cancer previously in almost moribund condition. On the other hand, our experience leads us to admit that a majority, despite the frequent enjoyment of a further period of symptomatic relief, fail to survive 12 months. This may in part be due to occasional failure to secure total pituitary ablation, and in this respect we welcome the modification suggested by Dr. Fraser and his colleagues for ensuring a suitable concentration of radioactive material in the appropriate area.

Nevertheless we feel it important that such treatment should be viewed in its right perspective lest a procedure of undoubted scientific interest, which apparently affords such a simple alternative to surgical hypophysectomy, should become overrated as a routine method of dealing with advanced cancer.

Institute of Urology,
London, W.C.2. J. D. FERGUSSON
J. J. STEVENSON.

SIR,—I read with interest the article by Professor Fraser and his colleagues.

In hypophysectomy the surgeon seeks to dissolve the integrity of the hypothalamus and pituitary gland by diathermy and section of the pituitary stalk, followed by removal and destruction of the pituitary gland itself. By this means he hopes for a total tumour recession in 24% of cases of metastasising neoplasm of the breast.

In many cases a portion of the pituitary gland, and the anterior lobe itself, projects through the diaphragm of the sella around the pituitary stalk, and indeed there may be functional pituitary cells in the stalk itself. This area is so important because, if there is continuity between the remaining functional cells and the hypothalamus, pituitary activity can subsequently be resumed. This is the very area where radio-active implants are the greatest danger and least effective.

In the past $3^3/_4$ years I have done over 100 hypophysectomies for metastasising breast cancer, and 24% of these have given full recession. By this is meant disappearance and healing of all deposits that are visible with the naked eye, palpable, or displayed radiographically. It is interesting that only 1 of these patients has subsequently died of breast cancer. The only 2 other deaths have been due to leukæmia in 1 case and to cortisone withdrawal following injury in the other. Symptomatic improvement may occur in those patients not falling into the full-recession group; but this is due to shrinkage of tumour, probably from fluid or crystalloid change, and does not in any way represent evidence of tumour recession. It is the 24% that get full recession which represent the surgeon's real hope.

Tests of pituitary function are difficult to assess, and assumptions from other glandular activity are most unsatisfactory. The urinary gonadotrophin activity may represent pituitary function, but it certainly does not follow the degree of recession in hypophysectomised patients.

I would want good evidence—and it should be sought—that full recession does occur in patients whose pituitary

1. *Brit. J. Urol.* 1957, **29**, 215.

gland is destroyed by implant methods. Some patients who do not do well after implants should have hypophysectomy performed with careful microscopic examination of a portion of the stalk removed at that time. This applies also to patients who break down following apparent improvement after implant treatment.

It has been said that hypophysectomy never cured a patient with metastasising breast cancer. We do not yet know whether this is true; and, until we do, surgical removal of the pituitary with full section of the stalk should be continued as the most likely method of obtaining full recession of tumour in patients with hormone-dependent neoplasm.

Birmingham. JACK SMALL.

NEW-TYPE OXYGEN CYLINDERS

SIR,—I sympathise with Dr. Eugene Thomas (March 14) over the difficulties he experienced with the 'Universal Handwheel' cylinder keys. I wonder if he has come across the 'Leytool' ratchet spanners, which I have been using for some months with complete satisfaction (and an absence of grazed knuckles) on a Walton mark-III gas apparatus. This spanner may be obtained to order with almost any size of ratchet insert; the one that is described as "$^1/_4$ in. across flats" is suitable for the older type of valve, but I imagine the makers could produce one on request for the new pattern. Although the spanner is only $4^1/_2$ in. long, the leverage is ample to turn the stiffest valve spindle with ease. A special spanner is, of course, still needed for the large hexagonal nut. Leytool spanners are manufactured by the Leytonstone Jig and Tool Company, Ltd., London, E.10.

Luton. J. C. PROSSER-FRENCH.

BRITISH MEDICAL STUDENTS' TRUST

SIR,—May we be allowed to draw your readers' attention to an appeal for funds now being made by the trustees of the above Trust?

The aims of the Trust are to give financial aid to medical students wishing to study abroad, and to defray the expenses of delegates sent to meetings of the International Federation of Medical Student Associations.

Until this year the student travel fund of the British Medical Students' Association made available what moneys it had to assist medical students to travel for study. The greater part of money for such travel has been provided by the students themselves, and although well over five hundred pounds have been distributed in four years this is small when compared with the requests for assistance. For this reason the British Medical Students' Trust has been established and is now launching an appeal to provide a capital sum to finance the above objects.

Over sixty students have in the past been assisted to travel for vocational reasons. In all cases they have first to obtain the consent and approval of their deans. They have attended courses of study at universities and hospitals in Europe, especially those in Scandinavia, and in the distant countries such as the U.S.A., Canada, Brazil, and Kenya. In taking part in such study courses these students have gained an early acquaintance with different philosophies and practice of medicine.

The British Medical Students' Association is a founder member of the International Federation of Medical Student Associations, a purely professional medical student body with a membership of approximately 180,000 students mostly from Commonwealth and European countries. This Federation receives the interest and support of the World Medical Association and the World Health Organisation. Great Britain has always taken an active interest in the counsels of the Federation and this year has the honour of being the chairman nation. The Trust makes provision to allow a limited amount of money each year to defray the expenses of B.M.S.A. delegates to the meetings of the I.F.M.S.A.

The Trust, as far as we are aware, is the first of its kind in this country, in that it has been established by undergraduates to aid undergraduate education and welfare.

The trustees hope that members of the medical profession may wish to contribute to this appeal; and contributions by gift or deed of covenant will be gratefully received by the Secretary, British Medical Students' Trust, B.M.A. House, Tavistock Square, London, W.C.1.

A. M. A. MOORE
Chairman of Trustees, Honorary President of B.M.S.A.

SOLOMON WAND
Trustee, Chairman of B.M.A. Council.

GRAHAM D. LISTER
Trustee, President, B.M.S.A.

Public Health

NATIONAL WATER RESOURCES

THE Central Advisory Water Committee has been taking stock of the water-supplies of England and Wales. Two of its subcommittees have reported. One[1] reviewed all the current activities which contribute to knowledge of the nation's water resources, and considered what more should be done, and how the information could be passed around. The other[2] had the more important task of investigating the extent to which the demand for water is increasing and is likely to increase still further; how to supply it, and what it will cost; and whether people could economise in its use, or cut the cost, without sacrificing their standards of hygiene or their industrial and agricultural efficiency.

The outcome of these deliberations are two very hesitant reports. Superficially they present a reassuring façade, but underneath they make it plain that all is not well with the water industry. The Coalition Government's white-paper in 1944 *A National Water Policy* overran subsequent political thought on the expediency of nationalising or rationalising more of the public utilities. The Central Advisory Water Committee was suspended from 1952 to 1955, ostensibly as an economy measure, and since its reconstitution has seemed to find difficulty in shaking off a feeling that it exists on sufferance. Hence no doubt the hesitancy of its subcommittees' reports. It has taken over three years to review the next six. It is disappointing to see that it was unable to make any serious attempt to assess our water demands beyond 1965. It is hard to believe that a great industry, with £30–£35 million per year of planned new capital expenditure, should feel incapable of looking more than six to ten years ahead to see where it is going.

On the other hand the Central Advisory Water Committee was honest to avoid wild guesses when it had not enough basic data to forecast beyond 1965. The lack was not its fault. When the committee was reassembled in 1955 it had to make almost a fresh start on the white-paper's declared first objective of collecting full informa-

1. Central Advisory Water Committee: report of subcommittee on information on water resources. H.M. Stationery Office, 1959. Pp. 20. 1*s.* 3*d.*
2. Central Advisory Water Committee: first report of subcommittee on the growing demand for water. H.M. Stationery Office. 1959. Pp. 28. 1*s.* 3*d.*

tion about the national water resources and the demands. It set about examining the practice and experience of the major statutory water undertakers in England and Wales, with the avowed object of making a balance-sheet of supply and demand. And a very rough one it is, even for the present day. For the future it is so highly speculative that it would be wise to think of the figures not so much as those of a balance-sheet as those of betting odds.

UNANSWERED QUESTIONS

There are two categories of water-supply—public and private. Similarly there are two main categories of use—domestic and industrial/agricultural. Each group displays ignorance of facts and uncertainties about the future.

Most of the public water-supplies have been reviewed in painstaking detail in the inland water surveys conducted by the engineering inspectors of the Ministry of Housing and Local Government—a valuable contribution to knowledge of present-day conditions in established water undertakings. We now have a clearer picture of how much water is being abstracted from each source and how much goes to waste, and some idea of how much more could be obtained. We know the water undertakers' long-term schemes for meeting their anticipated extra local calls, and have some measure of their neighbours' need for help. These inland water surveys have shown that there are enough undeveloped resources to meet the future requirements of the country as a whole on any scale yet envisaged. But that is where the problems start: means do not exist for supplying the country as a whole, and not enough imagination is being shown in studying the horizon.

The areas of high rainfall and impervious rock lie mainly in the geologically older hills of the west and north-west, where most of the water runs to waste unmeasured. In the south and south-east most of the rain soaks into the ground, but comparatively little is known about it. That is why the Central Advisory Water Committee is recommending the establishment of many more stations to record rain and snow falls, and why it is prodding the river boards to get on with the outstanding two-thirds of yet uncompleted river-gauges. But even if we do not know how much rain falls and how much runs to waste, we do know that the overground water storage capacity is about 200,000 million gallons in England and Wales, and 60,000 million gallons in Scotland. These reservoirs, however, are available to only a small handful of water undertakers, leaving the rest in a much more precarious position.

There is even less detailed knowledge about the underground resources in the great waterbearing strata of the chalk and the bunter sandstone, and all the minor aquifers elsewhere. H.M. Geological Survey have been collecting data on behalf of the Ministry of Housing and Local Government, and so the Central Advisory Water Committee urges that at least selected data should be published to help assessment of competing interests. If silent underground battles are going on between private and public pumping stations, it must surely be time to extend the statutory " controlled areas " for abstracting underground water.

PRESENT AND FUTURE DEMANDS

Turning to the demand for water, the committee estimates that this is now increasing by about 2% per year, and that the rate of increase is growing. Most of the increase is on the metered supplies—that is to say, on industrial and agricultural use rather than on domestic calls. Even so, the number of gallons per head per day is increasing disproportionately with the growth of the population. That reflects in part the very welcome post-war spread of piped water-supplies into rural areas, with waterborne sanitation, baths, and other improvements in general hygiene; only about 10% of the population are now without piped water. It also reflects a hidden volume of waste in the distribution systems—a subject on which the water undertakers are very sensitive.

Although the large cities' consumption ranges around 50–70 gallons per head per day, we are often told that many American cities exceed 100 gallons, and that this is a measure of their higher standard of living. It may well be due partly to their more carefree attitude to waste of consumer goods. We cannot afford to adopt all their ways, even with water at less than 1*s.* per ton delivered to our taps. It has long been a tempting financial manœuvre to attract extra capital for enlarging the headworks instead of cutting into revenue by repairing the pipes in the distribution system. Charges are so based that all consumers pay for every gallon lost, irrespective of whether they have a meter or not. But there must come a day when waste will no longer show a profit.

Nevertheless, it is the non-domestic demand for water that presents the more difficult problems. The older electricity generating stations need enormous quantities of water—according to one estimate, some 600 tons of water for each ton of coal used or about 15,000 million gallons per day in all.[3] Many of the newer atomic power stations, needing even more, have been sited to ease this burden; for cooling water need not necessarily be potable, and much of it may be available for re-use by someone else. Vast quantities are needed by the iron and steel and chemical industries; so that possibilities of re-use are well worth notice. The Central Advisory Water Committee seeks much more information on the re-use of water within factories, along the line of a river, or by return to the underground aquifers after safeguarding against harmful pollution. That might offer many rewarding economies in our industrial calls for water.

Growth in agricultural demands could be more serious still.

The increased use of water in the production of tuberculin-tested milk, washing down, and cooling has already upset the efficiency of many of our smaller rural systems, not only in winter when the cattle are indoors but also in summer with heavy wastage from field troughs. These conventional uses in agriculture can no doubt be met by adapting our present resources, but if irrigation of land becomes more prevalent it could easily wreck all calculations. It was estimated[4] last year that some 60,000 acres of land are already under spray irrigation, and almost all that water was evaporated or transpired in plant growth and so was not available for re-use. The Central Advisory Water Committee suggests that most agricultural land south of the Humber-Severn line would benefit from irrigation to improve the crop yields. That would need about 8000 million gallons in dry years. The Ministry of Agriculture, Fisheries, and Food estimates that on the present rate of development in soil irrigation we may need some 240 million gallons per day to meet the peak demand in a dry year. Much of the water now being taken for that purpose comes from the rivers, and already causes embarrassment to river boards, water undertakers downstream, and fisheries. This has to be weighed against such factors as another two tons of potatoes per acre.

The Central Advisory Water Committee strongly recommends that statutory powers should be sought to control the abstraction of surface waters as well as underground reserves. This seems fully justified when we are

3. Balchin, W. G. V. *Times*, June 24, 1957.
4. Whitaker, A. *ibid.* Sept. 17, 1958.

told that irrigation demands could exceed all industrial and domestic use combined.

CONTROL

The responsibility for the conservation and allocation of our water rests upon the Minister of Housing and Local Government, under the Water Act of 1945. The Central Advisory Water Committee is doing its best to help him in the primary tasks of assessing the national resources and making even this limited attempt to estimate the country's future needs. Perhaps we can expect further reports to carry things forward. On the doubtful assumption that there will be enough water for everyone wherever they want it, future gathering-grounds and reservoir sites could be reserved under planning legislation, and the extension schemes prepared in outline against the time when they may be wanted. A more critical attitude to waste is not an unreasonable demand by the countryman before some conurbation seeks compulsory powers to drown his valley. A more rational effort at flood control, and a more careful balance between land-drainage interests and water-handlers, would help.

If contentious housing rents could be tackled by a Government, surely so can water. The regrouping of more than a thousand separate public water undertakers down to some 300 or less is a step ahead—a very faltering step by reluctant bedfellows-to-be. Yet might this not have been better done from the other end? Surely the obvious way to reorganise the water industry efficiently is to base it upon the 18 hydrometric areas in England and Wales, with administrative functions analogous to the regional hospital boards, and then coalesce the present 32 river boards to fit that geographical structure. Such an arrangement would coordinate for each natural region all the meteorological services, land-drainage interests, river boards, and surface and underground water users and re-users, including sewage and industrial waste disposal. Below the 18 regional (hydrometric) boards could logically be placed local water groups, analogous again to our hospital management committees, formed to coordinate those same factors in areas of natural sympathy, and to undertake the specialised and skilled duties of executive management of the several local undertakings scattered throughout their territory.

Perhaps this may be the idea behind the present pressure to regroup, but it will need very careful guidance to make sure that the new groups now being formed will be capable of absorption into some future wider administrative network that alone can offer a sane basis for sharing what water we have. The Central Advisory Water Committee has plenty of scope for further thought.

Smallpox in Liverpool

A 21-year-old medical student of Liverpool University was admitted to hospital on March 7 with smallpox. He fell ill on Feb. 28. The infection is mild and he is doing well. Some of his clothing had been sent to a laundry, which has been closed. There were many contacts and this week will be the critical one in which the disease may appear in others. Customers of the laundry and fellow students of the patient are among those who have been vaccinated.

Influenza

The outbreak of influenza is subsiding generally. In England and Wales in the week ended March 7 deaths from this cause numbered 1399, compared with 54, 144, 455, 1121, and 1571 in the four weeks from that ended Jan. 31 to that ended Feb. 28.

Notes and News

NEW HOSPITALS IN WESTERN GERMANY

AN account of a tour of some hospitals in Western Germany [1] last summer brings out the fact that many of our hospital problems exist elsewhere. Over 200 members of the International Hospital Federation, from 20 different countries, spent eleven days touring a wide area of the Federal Republic. They saw ten hospitals, almost all built in the past few years.

The report includes two German articles on present-day hospital problems. The remedies proposed for shortage of medical, nursing, and technical staff are similar to those suggested in this country: the creation of more consultant posts is envisaged, and it is thought that nursing recruitment would be helped by having more mechanical aids and by raising social status and pay. Two interesting sidelights throw the stresses and strains into sharper relief:

(1) The legal working week for nurses is 60 hours, but most hospitals have succeeded in reducing this to a 54-hour or even a 51-hour week.

(2) The junior medical staff of many hospitals has made claims for paid overtime, and these are to be contested in the labour courts.

Besides these difficulties there are those caused by the tripartite provision of hospitals (public, voluntary, and private) and Federal control of hospital charges. These charges are related to prime costs only, and the Federal, State, and social-insurance authorities have not been able to agree on the responsibility for the deficit on building and maintenance. The term "the 'sick' hospital" has been coined, and it is evident that early and drastic treatment is necessary.

When the group were asked for their final impressions, a Scottish participant thought that patients' rooms were cramped in comparison with the large halls, corridors, and day-rooms; whereas an American regarded the rooms and wards as wastefully large. All agreed, however, in envying the lavish provision of television cameras in operating-theatres, with separate viewing-rooms, and the exciting possibilities of designing furnishings, equipment, and decoration for a new hospital as a single coordinated whole.

FAMILY PLANNING ASSOCIATION

AT a meeting on March 10 the film *Birthright*, which was commissioned by the Association, was shown for the first time. Its theme is the unhappiness that ignorance can bring, and it illustrates the work of medical and lay workers in the Association. Afterwards, Sir Julian Huxley and Dr. A. S. Parkes reported on the proceedings of the recent International Planned Parenthood Federation conference at Delhi. Dr. Parkes emphasised that the present imbalance between the birth-rate and the death-rate is a demographic emergency. Research on simpler contraceptives had been reported at the conference, but in his view there was still no oral contraceptive which was clinically useful.

FIRST AID IN INDUSTRY

THE I.C.I. first-aid competition last week was an enjoyable, instructive, and impressive busman's holiday. The realism of the tests was astonishing. There was a crash and a yell and the stage curtains parted to disclose to the team competitors a ship tied up to massive bollards on a dock. Distant ships hooted and seamews skreighed (anglice—squawked—a less elegant word). A seaman lay on the deck with his spine fractured by a crate. As the team got on the job one was struck by the impassiveness of the ship's master looking out of the wheelhouse. His interest appeared quite academic; and indeed it was, for the bowler hat, duffel coat, and ferocious red beard disguised one of the best-known medical examiners in the St. John organisation. Individual tests were equally realistic, and a fine epileptic fit was thrown by one casualty, who also burned her hand on a stove and upset a rice pudding (conveniently enough on a sheet of plastic). Bouquets were deserved

1. Report of Study Tour of Hospitals in the German Federal Republic, June 3–14, 1958. International Hospital Federation, 34, King Street, London, E.C.2. 1958. Pp. 89. Price 8s. to members of the Federation; 10s. to non-members.

all round—for the medical staff, the organiser, the casualties who acted so well, the official who approved the considerable expenditure, and not least the competitors. The gentleness with which most of them did their work was impressive; among the twelve teams surely there were several good G.P.'s manqué.

First-aid training is valuable in all kinds of situations, but it is particularly important in industry as indeed most employers recognise. To accord it this amount of attention and encouragement must have a stimulating influence outside as well as inside the company.

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names:

Approved name	*Other names*
Azapetine	1-Allyl-2:7-dihydro-3:4-5:6-dibenzazepine Ilidar is the phosphate
Calcium Benzamidosalicylate	Calcium 4-benzamido-2-hydroxybenzoate Aminacyl B-PAS; Therapas
Dexamethasone	9α-Fluoro-11β:17α:21-trihydroxy-16α-methylpregna-1:4-diene-3:20-dione 9α-Fluoro-16α-methylprednisolone Decadron; Deronil; Dexacortisyl is the 21-acetate
Dimenoxadole	2-Dimethylaminoethyl α-ethoxy-αα-diphenylacetate
Ditophal	Diethyl dithiol*iso*phthalate Etisul
Fluopromazine	10-(3-Dimethylaminopropyl)-2-trifluoromethyl-phenothiazine Vespral is the hydrochloride; Vesprin is the hydrochloride
Hydrochlorothiazide	6-Chloro-3:4-dihydro-7-sulphamoylbenzo-1:2:4-thiadiazine 1:1-dioxide Esidrex; Hydro-Saluric
Hydroflumethiazide	3:4-Dihydro-7-sulphamoyl-6-trifluoromethylbenzo-1:2:4-thiadiazine 1:1-dioxide Hydrenox: Naclex; Rontyl
Mebhydrolin	5-Benzyl-1:2:3:4-tetrahydro-2-methylpyrid-[4,3-b]indole Incidal is the naphthalene-1:5-disulphonate
Methylchromone	3-Methylchromone Crodimyl
Norcodeine	*N*-Demethyl codeine
Normorphine	*N*-Demethyl morphine
Orphenadrine	2-Dimethylaminoethyl-2-methyldiphenylmethyl ether Disipal is the hydrochloride
Phenmetrazine	Tetrahydro-3-methyl-2-phenyl-1:4-oxazine Preludin
Pipamazine	10-[3-(4-Carbamoylpiperidino)propyl]-2-chlorophenothiazine
Prothipendyl	10-(3-Dimethylaminopropyl)-9-thia-1:10-diaza-anthracene Phrenotropin is the hydrochloride
Sulphasalazine	4-Hydroxy-4¹-(pyrid-2-ylsulphamoyl)azobenzene-3-carboxylic acid Salazopyrin
Thiambutosine	*N*-*p*-Butoxyphenyl-*N*¹-*p*-dimethylaminophenylthiourea 4-Butoxy-4¹-dimethylaminodiphenylthiourea Ciba 1906
Thiotepa	Tri-1-aziridinylphosphine sulphide Triethylene thiophosphoramide

INDEX

Proprietary name	*Approved name reference*
Aminacyl B-PAS	Calcium Benzamidosalicylate
Ciba 1906	Thiambutosine
Crodimyl	Methylchromone
Decadron	Dexamethasone
Deronil	Dexamethasone
Dexacortisyl	Dexamethasone
Disipal	Orphenadrine
Esidrex	Hydrochlorothiazide
Etisul	Ditophal
Hydrenox	Hydroflumethiazide
Hydro-Saluric	Hydrochlorothiazide
Ilidar	Azapetine
Incidal	Mebhydrolin
Naclex	Hydroflumethiazide
Phrenotropin	Prothipendyl
Preludin	Phenmetrazine
Rontyl	Hydroflumethiazide
Salazopyrin	Sulphasalazine
Therapas	Calcium Benzamidosalicylate
Vespral	Fluopromazine
Vesprin	Fluopromazine

CLOSED-CIRCUIT TELEVISION CONFERENCE

DEMONSTRATIONS of surgical and clinical procedures, presented by the North Middlesex Hospital, were shown by television to medical audiences in a London cinema on March 9–12. A feature of the programmes was the variety of topics shown—operative surgery occupied only a quarter of the time. In one programme film was shown on the same screen as the television, so the quality of the two could be directly compared. Three television cameras were used for the demonstrations—one colour and two black-and-white. As is now usual in this type of conference, the surgeon in the theatre and the panel members in the temporary studio at the hospital could be heard by the audience, and a moderator in the hall could speak directly to either, and relay questions from the audience to those taking part.

The first programme was devoted to a symposium on mitral stenosis. The panel included Sir Russell Brock, Dr. Paul Wood, Dr. W. Doherty, and Mr. A. W. Purdie; and a mitral valvotomy was demonstrated from the theatre, where the colour camera was installed, by Mr. Michael Bates and Mr. Raymond Hurt. The opening stages of the operation, an animated sequence showing the commisurotomy, and finally the closing stages were shown on film in the hall.

In the second programme Dr. Norman Whittaker discussed the early diagnosis of diabetic coma; Dr. C. Allan Birch, Mr. Keith Moore, and Mr. T. E. Broadbent discussed dysphagia; and Mr. Basil Page demonstrated a partial nephrectomy for stone while Mr. Marco Caine described the stages of the operation with diagrams, and discussed the features of it with Sir Eric Riches.

For the third programme the colour camera was installed with the others in the temporary studio. Dr. R. Kempthorne and Dr. W. Dangerfield discussed recent views on cholesterol, fat, and coronary thrombosis; Dr. J. H. Jacobs gave a demonstration of electromyography in the diagnosis of neuromuscular disorders; and Dr. John Dalziell interviewed Dr. E. C. O. Jewesbury on some practical problems in epilepsy. Finally Dr. Michael Feiwal introduced some patients and suggested a new approach to dermatology.

The final programme consisted of a demonstration of modified electroplexy by Dr. E. B. Strauss and Dr. S. Bockner, and a discussion on the management of toxic goitre between Dr. A. W. Spence, Prof. T. Russell Fraser, and Dr. T. Ferriman, with the operation demonstrated by Mr. T. M. Hennebry.

As on earlier occasions[1] the clinical demonstrations, especially those in which good use was made of visual aids, were of greater interest to the audience than the surgery. Only part of each programme was in colour. The quality of the colour television improved gradually during the demonstrations and on the third and fourth nights was quite acceptable, though the extremely limited depth of focus of the colour camera when used for close shots made the operation scenes barely adequate. In the film sequences the advantage of 16 mm. film was well demonstrated. Certainly five hundred doctors would not have attended on each of four nights had a programme only of films been shown; but a film, produced at a fraction of the cost of a television demonstration, would probably be seen by a larger audience in its lifetime.

University of Cambridge

On March 7 the following degrees were conferred:

M.A.—Cicily M. Clarke.
M.Chir.—*P. S. Reay-Young.
M.B., B.Chir.—Anthony Kenyon.
M.B.—*P. W. Clements, G. E. T. Raine.

*By proxy.

Sir Lionel Whitby medal—To commemorate the name of Sir Lionel Whitby in the Cambridge Medical School, Lady Whitby and her family have offered a medal to be awarded annually for an M.D. thesis of exceptional merit which deals with investigation carried out in the laboratory, preferably on a hæmatological subject.

1. See *Lancet*, 1957, i, 1078.

University of Reading

On May 9 the honorary degree of D.SC. will be conferred on Sir Paul Fildes.

University of St. Andrews

On June 30 the honorary degree of LL.D will be conferred on Sir Lindor Brown and Prof. D. K. Dow.

Royal College of Physicians of London

On Tuesday and Thursday, April 14 and 16, at 5 P.M. at the college, Pall Mall East, S.W.1, Prof. E. J. Wayne will give the Lumleian lectures. His subject will be clinical and metabolic studies in thyroid disease.

Royal College of Surgeons of England

At a meeting of the council on March 12, with Sir James Paterson Ross, the president, in the chair, Mr. G. H. Macnab was admitted to the court of examiners. Mr. Gordon Paul was admitted to the fellowship *ad eundem*. Diplomas of membership were granted to B. H. Ackers and M. D. Sanders.

Faculty of Anæsthetists.—Dr. R. P. W. Shackleton and Dr B. L. S. Murtagh have been elected members of the board of the faculty. The fellowship was granted to D. B. Benzon, F. W. Pais, and W. M. Wilkinson.

On Wednesday, April 8, at 5 P.M., at the college, Lincoln's Inn Fields, London, W.C.2, Sir Clement Price Thomas will give a Tudor Edwards lecture. His subject will be conservative and extensive resection for carcinoma of the lung.

William Mackenzie Lecture

On Friday, April 3, at 5 P.M., at the Faculty of Physicians and Surgeons, 242, St. Vincent Street, Glasgow, Prof. I. C. Michaelson, from the Hadassah Hebrew University, Jerusalem, will give this lecture. His subject will be error and discovery in fundal disease.

College of General Practitioners

Public Welfare Foundation Prize.—Six prizes (£40 each) are offered to senior medical students in the United Kingdom and Eire, who have discussed the diagnosis and management of patients in the setting of general practice.

The student should have been introduced to the patient by the family doctor, he should have seen the patient on at least three occasions in the doctor's consulting-room or in the patient's home, and he must have discussed with the doctor the relevant clinical and social factors. Details and application forms may be had from the dean of the student's medical school or from the secretary of the college, 41, Cadogan Gardens, London, S.W.3. The closing date is Aug. 1.

South West Metropolitan Regional Hospital Board

The following have been awarded prizes in the board's 1958 competition:

Consultants and S.H.M.O.s.—Dr. J. Foley, Dr. J. Gibson, Dr. M. M. Glatt, Dr. R. J. Hamer Hodges, Dr. B. H. Kirman and Dr. C. E. Williams (joint entry), Dr. F. A. Nash.

Senior registrars, registrars, and J.H.M.O.s.—Dr. J. M. Berg, Dr. John M. Ponsford, Dr. M. M. Rao, Dr. P. E. Sylvester.

Senior house-officers and house-officers.—Dr. G. E. Fulford, Dr. R. J. Jarrett.

Medical Society of London

At the 179th anniversary dinner of this society on March 12, Lord Cohen of Walmer said that the National Health Service represented an advance, for without it the voluntary hospitals would have become bankrupt or at least inefficient; but he doubted whether, even now, enough was being spent on rebuilding obsolete hospitals. As regards the administrative burden on hospital staffs, committees could not, in his view, be reduced; but he believed that this burden could be eased by reducing the number of circulars and forms. Responding to Lord Cohen's toast of The Society, Dr. E. R. Cullinan, the president, reported that the meetings had been well attended, and that the finances were sound. Dr. J. Bishop Harman spoke "in honour, praise, and welcome" of the guests; and in a poetical reply Prof. A. M. Claye, P.R.C.O.G., reflected:

> "It makes it easier to be terse
> When what one says is couched in verse."

Association of Surgeons of Great Britain and Ireland

The annual meeting of this Association will be held from April 23 to 25, at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2. The programme will include a Moynihan lecture on Friday, 24th, at 4.30 P.M., when Prof. J. H. Louw will speak on the pathogenesis and treatment of congenital intestinal atresia.

Mental Retardation

An international conference on this subject will be held from July 27 to 31 in Portland, Maine. The English speakers will include Prof. J. N. Cumings. Further particulars may be had from Dr. Ella Langer, c/o Eastland Hotel, Portland, Maine, U.S.A.

Royal Statistical Society

The medical section of this society will hold a conference at Bedford College, Regent's Park, London, N.W.1, on Friday, April 17. The subjects chosen for discussion are accidents and medical genetics. Further particulars and tickets (15s.) may be had from the hon. secretary of the section, Mr. J. A. Heady, Social Medicine Research Unit, London Hospital Research Laboratories, Ashfield Street, E.1.

A meeting for general practitioners will be held on Sunday, April 5, at 10.15 A.M., at University College Hospital, London, W.C.1. Mr. D. P. Greaves and Mr. C. Dee Shapland will speak on eye conditions commonly met in general practice.

The annual general meeting of the Auxiliary Royal Army Medical Corps Funds will be held on Monday, April 6, at 5 P.M., at 11, Chandos Street, London, W.1.

The Yorkshire Thoracic Society will hold a meeting on Friday, April 10, at 5.30 P.M., in Leeds General Infirmary. Dr. Paul Wood will speak on modern auscultation.

Diary of the Week

MARCH 22 TO 28

Monday, 23rd

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Prof. Arnold Sorsby: Irregularly Dominant Affections of the Retina.

BRITISH ASSOCIATION OF SPORT AND MEDICINE
5.30 P.M. (Guy's Hospital Medical School, S.E.1.) Dr. Jack Joseph: Anatomy of Movement in Relation to Athletes.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine.* Prof. E. A. Pask, Dr. Hugh Garland, Mr. Walpole Lewin: Management of Prolonged Unconsciousness.

Wednesday, 25th

UNIVERSITY COLLEGE, Gower Street, W.C.1
5.30 P.M. Dr. Valy Menkin (Philadelphia): The Role of Inflammation in Carcinogenesis.

ROYAL SOCIETY OF MEDICINE
8.30 P.M. Sir John Cockcroft: Peaceful Uses of Atomic Energy. (Lloyd Roberts lecture.)

BRITISH PSYCHOLOGICAL SOCIETY
8.30 P.M. (11, Chandos Street, W.1.) *Medical Section.* Mr. Michael Reed: Communication and the Deaf.

MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) *Medicine.* Dr. Shirley Smith: Recurrent Angina Independent of Effort.

Appointments

ALLEN, MARJORIE, J. G., M.B. Edin., D.P.H.: assistant M.O., Surrey.

DAVY, B. W., M.D. Lond., D.P.H., D.P.M.: consultant psychiatrist with a major interest in problems of student mental health, United Cambridge Hospitals.

LUDKIN, STANLEY, M.D. Durh., D.P.H.: deputy M.O.H., Co. Durham.

TAPP, GWENDOLYN R., M.B. Lond., D.C.H., D.P.H.: assistant M.O., Surrey.

TAYLOR, W. H., D.M. Oxon., M.R.C.P.: consultant chemical pathologist, United Liverpool Hospitals.

WILLIAMS, E. A., M.B. Lond., F.R.C.S., M.R.C.O.G.: consultant obstetrician and gynæcologist, Newport and East Monmouthshire and North Monmouthshire H.M.C. areas.